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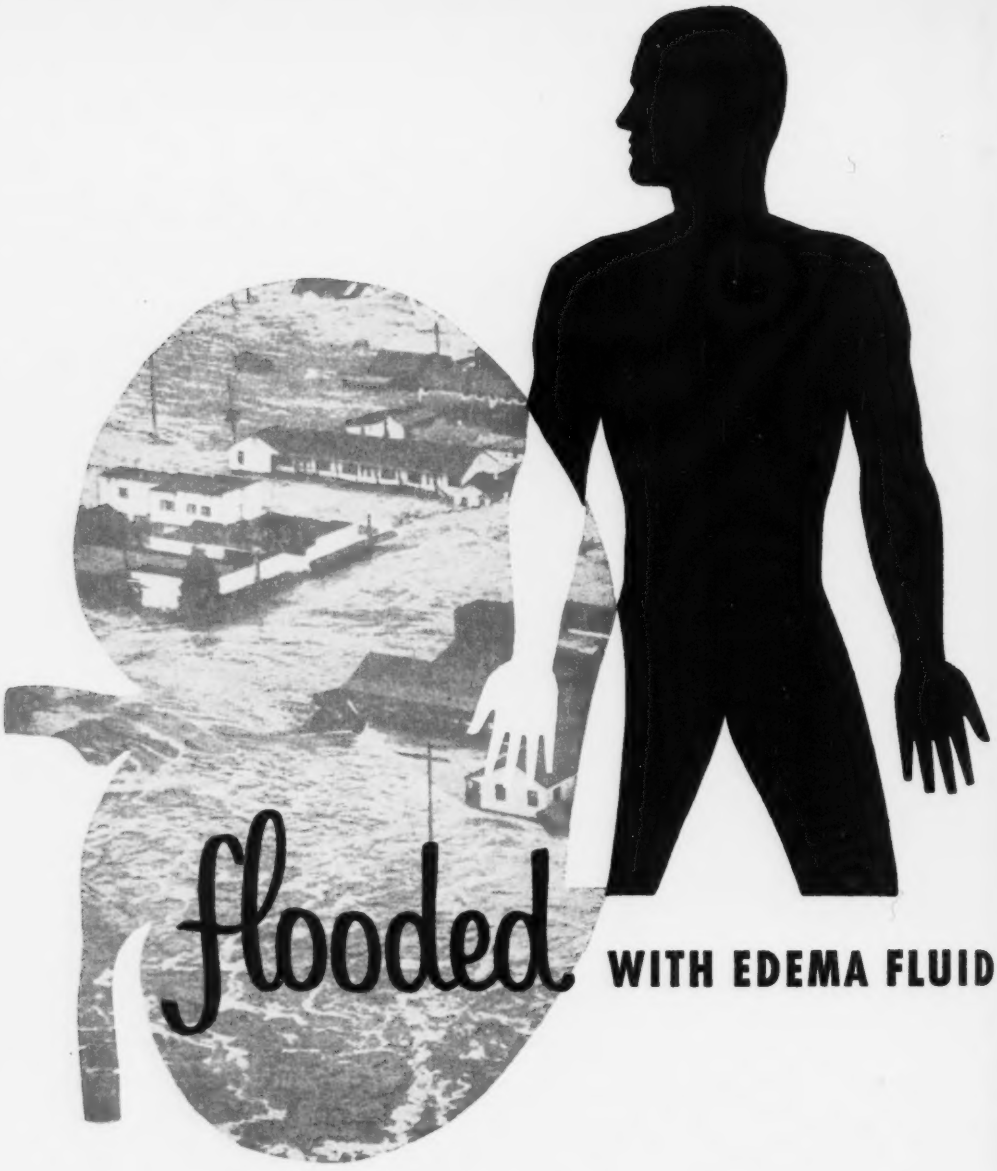

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Editorial

Dietary Fats and Their Relationship to Atherosclerosis

THE remarkable increase in life span of the people of these United States can be attributed in general to increased medical knowledge and more especially to improved sanitation and nutrition. The chemotherapeutic agents and other specific measures have tended to relieve the physicians from focusing their attention on the acute episodes of medicine. This has allowed them to intensify their interest in the phenomena of the so-called chronic diseases.

Atherosclerosis, the chronic disease under present discussion, in all probability has no single cause. Those presently implicated are heredity, anatomy of the blood vessel wall, arterial blood pressure, diet, lipid content of the blood, sex, and others.

There is increasing recognition that health and disease are biologic expressions of the reaction of man to his environment. Three elements must be analyzed in interpreting the course of mass disease, environment, host, and agent of disease.

The diet contributes to the internal environment of the body, hence it may be directly connected with the development of atherosclerosis. Fat is commonly referred to as the dietary culprit and many physicians, when they hear the terms dietary fat and cholesterol, think that they are synonymous with atherogenesis and arteriosclerotic heart disease.

The epidemiology of atherosclerotic heart disease is at present unknown. Various attempts have been made to study this problem. Ciocco[1] states:

> In brief, we have yet to develop analytical procedures for long term studies that will allow us to make adjustments for possible interactions between the incidence of the disease condition on one hand and refusals, migrations, and morbidity and mortality from other disease conditions on the other, and thus allow us to estimate the true incidence of a disease condition. Until this development is accomplished, comparisons of incidence rates, from place to place, or interpretations of relationships between incident rate and possible etiological factors have to be accepted with several grains of salt.

From the dietary point of view, one runs into a great many problems in attempting to assess the nutrient intake of individuals in a mass population. National food balances and other similar types of dietary surveys have proven hopelessly inadequate in this respect.

The present focal point of interest in the diet and its relationship to atherosclerosis is dietary fat. Dietary fat is a mixture of fatty acids, steroids, and other substances of similar nature. Fats from animal and vegetable sources differ in their composition. Not only are the different types of fats involved in the present study but also the total amount of fat. One cannot separate the study of the fats from the total caloric intake. This involves all the other foods consumed as well as the activity or energy expenditure factors of the individual which make up the balance. The ingestion of an excessive amount of calories will lead to obesity. The body is perfectly capable of synthesizing fat from the other food stuffs. It has been shown that mortality rates per se tend to rise with degrees of overweight; this is particularly marked among the younger overweight persons.

From New York University Post-Graduate School of Medicine.

The possibility remains that the kind, rather than the amount of fat in the diet is responsible for atherosclerosis. Much time has been spent in studying vegetarian versus nonvegetarian groups. No critical results have been made available. The reported effect of vegetable fats and their content of unsaturated essential fatty acids is also of extreme interest in this connection.

One of the major problems under discussion is whether there has been a marked change in the American diet during the past generations—the period in which the incidence of coronary heart disease and atherosclerosis is said to have increased.

Many of the conclusions that have been reached are subject to very basic criticism. It is very important that physicians realize that the urgency of the situation does not permit the disruption of a sound and orderly attack on the problem by undue emotionalism and competitiveness among the investigators. Altering the dietary habits of a large population group is fraught with a great many dangers. Our knowledge of nutrition is not sufficient at this time to anticipate what ultimate results would happen if the public were encouraged to alter radically their basic dietary patterns.

It is indeed to be hoped that current experimental work in laboratories all over the world will make it possible to provide further information on these very important problems. It will be a long time before this area is completely clarified, but as data are published they should place some limits on the areas of speculation. The physician must continue to try to view and review this subject as objectively as possible.

HERBERT POLLACK

REFERENCE

[1] CIOCCO, A.: Implications to the bio-statistician. Am. J. Pub. Health **47:** 58, 1957.

Who will perswade a man that has not tasted them, that sweet or new wine is better than water? with what arguments shall one perswade a blind man that the Sun is clear, and out-shines all the Stars in the firmament? So concerning the Circulation of the blood, which all have had confirm'd to them for so many years, by so many ocular experiments, there has been hitherto no man found, who by his observations could refute a thing so obvious to the sense (to wit the motion of flux and reflux) by observations alike obvious to the sense, or destroy the confirm'd experience of it, nay by ocular testimony none ever offer'd to build up a contrary opinion.

—WILLIAM HARVEY, *De Circulatione Sanguinis*, 1649.

Atherosclerosis and the Fat Content of the Diet

By Irvine H. Page, M.D., Fredrick J. Stare, M.D., A. C. Corcoran, M.D., Herbert Pollack, M.D., and Charles F. Wilkinson, Jr., M.D.

A report to the American Heart Association and to the American Society for the Study of Arteriosclerosis the Nutrition Committee of the Council on Community Service and Education of the American Heart Association and others.

THE aim of this discussion is to summarize and evaluate evidence for and against the concept that the fat content of the average present-day North American or north European diet is a significant factor in the genesis of cerebral, myocardial, renal, or peripheral atherosclerosis. To date there is no incontrovertible evidence for such a relationship; nevertheless, a strong case is developing to suggest that the nutritional status of an individual is an important environmental factor in the etiology of this disorder. The total fat and the type of fat in the diet are among the nutritional factors particularly involved.

General Principles

A review of this kind may provide nutritionists and physicians with a guide when health recommendations are made to groups or to individuals. In formulating these recommendations, however, one must always bear in mind that the results of clinical studies on patients and experimental studies on animals are not necessarily applicable to healthy individuals.

It is hoped that industries concerned with the manufacture, processing, and distribution of foods and the insurance industry, will take responsibility for performing and promoting effective basic as well as applied research on the problem of the relationship between diet and atherosclerosis. Industry is usually generous in the support of research for product development. It has given very limited support to basic research in this vital field, even though the results of such investigative work would enable management to plan more intelligently for the future. The need for reliable information and appropriate action is urgent.

One of the first things that occur to lay individuals in thinking about chronic diseases is a possible change in diet. Frequently this reasoning is applied to situations in which diet is of little or no importance. The result is a flood of diet fads and quackery. In the case of atherosclerosis, there is some evidence that diet may be of considerable importance. It is now the responsibility of research workers to determine more exactly this possible role of diet in the etiology of atherosclerosis.

Atherosclerosis in all probability has no single cause. It results most likely from a combination of factors, or is, as Page[1] suggests, a "multifaceted disease." Among those facets presently implicated are heredity, diet, morphologic and chemical anatomy of the blood vessel wall, arterial blood pressure, lipid content of the blood, and sex. Atherosclerosis is a focal lesion. Because its consequences are widely variable, there is no practical means of clinical diagnosis of the uncomplicated, potentially reversible lesions. A large plaque may be so located as to cause little injury and a small one may be placed so strategically in a coronary vessel as to cause death by direct occlusion. Atherosclerosis is believed by some investigators to be episodic, with the plaques building up rapidly in days or weeks and remaining quiescent for months or years thereafter. Many workers believe this process to be reversible, at least in its early stages.

The approach to the problem by animal experiments has shown that atherosclerosis, similar to but not identical with that of the human type, can be produced in a variety of experimental animals by dietary variations. Many kinds of diets have been used; some are deficient in one or more nutrients, others contain excessive amounts of certain constituents or combine excess of one with deficiency of another. The results of such experiments have influenced significantly the opinions of clinicians about diet.

Various types of dietary surveys have been conducted in the United States and in other countries to determine if a relationship exists between diet and atherosclerotic coronary artery disease. The importance of the evidence derived from these epidemiologic approaches and its seemingly obvious implications justifies a critical evaluation of this phase of the problem.

The opinions of clinicians vary greatly. Some hold in high favor the view that atherogenesis and the lipid or cholesterol content of the blood are related directly. There is evidence both for and against this view. The most cogent evidence presented in favor of the serum lipid theory is that hyperlipemia over a sufficient length of time usually is associated with premature atherosclerosis. The first question raised concerns the concentration of plasma lipids that constitutes an abnormal elevation. Are the present normal standards and ranges biologically optimal? Or are they normal only for the North American population, a large proportion of which has premature or latent atherosclerosis? If the relationship between hyperlipemia and atherosclerosis is one of cause and effect, it follows that any regime that will reduce even "normal" blood lipid concentrations should also decrease the incidence of atherosclerosis. Is reduction of dietary fat or change in its type the only practical means of accomplishing this? And will it be effective?

More recently, evidence has been presented that the degree of unsaturation of fat in the diet and, in particular, the essential fatty acid content of the diet in proportion to total dietary fat may be of critical importance in determining the level of cholesterol and associate lipids in blood.

Another important aspect of the problem of coronary occlusion and its relationship to atherosclerosis of the coronary vessels is the possibility that the thrombosis is due more to a defect in the clotting mechanism than to an "incidental" coronary atherosclerosis. Defects of clotting mechanisms have been related by some workers to the fat content of the diet. Even the atherosclerotic plaques themselves have been related to abnormal clotting rather than to primary deposition of lipids. These alternatives are mentioned to illustrate the danger in taking too narrow a view of the problem in our concern with dietary fat and the mechanisms that may relate it to atherogenesis.

Most of the investigation of atherosclerosis must be done of necessity with animals. No clinical, objective method of antemortem diagnosis of uncomplicated atherosclerosis is available. This fact must be kept in mind when reading the clinical literature.

This is a time when great pressure is being put on physicians to do something about the reported increased death rate from heart attacks in relatively young people. People want to know whether they are eating themselves into premature heart disease. They are entitled to an unprejudiced answer. On the one hand, some scientists have taken uncompromising stands based on evidence that does not stand up under critical examination; on the other, certain industrial groups appear to believe they can suppress the problem by advertising campaigns. The current spate of articles in the lay press often does not present a balanced account of current opinion.

In the opinion of the authors of this review, there is not enough evidence available to permit a rigid stand on what the relationship is between nutrition, particularly the fat content of the diet, and atherosclerosis and coronary heart disease. We are certain of one thing: the evidence now in existence justifies the most thorough investigation. This should be done soon, thoroughly, and uncompromisingly.

Many nutrients, either in excessive, or in insufficient amounts, have been implicated in the pathogenesis of atherosclerosis. Fats, alone or in association with cholesterol,[1-8] have been given most attention, but intakes of protein, carbohydrate,[9] choline,[10] pyridoxine,[11] and organic sulfur[7] also have been implicated in atherogenesis, although largely from the aspect of their relationships to fat and cholesterol metabolism. Fat is certainly the central issue of both basic and clinical investigation and, now, also of lay speculation. This association

of fat with atherosclerosis has been pursued in nearly every part of the world and at various levels, epidemiologic, clinical, and experimental. No attempt will be made to document all of the evidence but rather to point out some of the seemingly significant directions it has taken, with the aim of formulating some interim conclusions.

Epidemiologic Approach

The starting point of this approach is the assumption that data are available that can convincingly show the association, or lack of association, between diet and especially coronary and cerebral artery disease. Some of the difficulties of determining the prevalence and severity of coronary atherosclerosis are indicated above and have been summarized elsewhere.[12] The clinical diagnosis of coronary arterial heart disease dates substantially from the first decade of this century. No one questions the remarkable increase in the *reported* number of cases of this condition. Undoubtedly the wide use of the electrocardiogram in confirming clinical diagnosis and the inclusion in 1949 of Arteriosclerotic Heart Disease in the International List of Causes of Death play a role in what is often believed to be an actual increased "prevalance" of this disease. Further, in one year, 1948 to 1949, the effect of this revision was to raise coronary disease death rates by about 20 per cent for white males and about 35 per cent for white females. Lew[13] states:

> In fact 30 per cent of the increase in the crude death rate from coronary artery disease since 1940 is due merely to the aging of the population. Another 40 per cent of the increase in the crude death rate can be ascribed directly to the changes in procedures and classification adopted with the sixth revision of the International Causes of Death. In my judgment, a major part of the remaining 30 per cent represents merely the acceptance of a broader concept of coronary artery disease, better diagnosis and increasing usage of the certifying causes of death. In other words, probably less than 15 per cent of the increase in death rate can be attributed to a real increase in the mortality from this disease.

Nearly a third of the reported cases of arteriosclerotic heart disease show a disparity between clinical and autopsy diagnosis, in part attributable to the wide range of subclinical coronary atherosclerosis. Hence, some statisticians do not accept the proposition that, in this country at least, there is an increasing incidence of this condition; others believe that such may be the case, particularly in younger age groups.

These difficulties in interpretation of the vital statistics occur even when the area under study is a single community. They become magnified as the area of study widens. Thus, a comparison of the 1950 vital statistics of the United States and Italy for the age group 50 to 54 shows wide differences.[14] In the United States cerebrovascular lesions would seem to be 10 (females) to 16 (males) per cent less common than in Italy, while in the United States degenerative heart disease (coronary, angina pectoris, myocardial infarction) is 3 times more common in males and 1.5 times more common in females. Ill-defined causes of death are more common in Italy than in the United States. Clearly, differences in diagnosis and certification between 2 countries account for some of these differences.

The unexpected finding is that like differences also arise between different parts of the United States, and even between neighboring states.[15] For example, the age-adjusted cardiovascular disease rate for 35- to 64-year-old white males indicates a spread from 348 (South Dakota) to 734 (District of Columbia) and from 550 (Virginia) to 668 (Maryland) and from 395 (Arkansas) to 524 (Alabama). In the specific case of coronary artery disease, the distribution of deaths in the United States assumes a geographic pattern with maxima in the Middle Atlantic States and California and minima in the East South Central States.[16] The highest rate occurs in New York and the lowest in New Mexico. The meaning of these differences is obscure. The data show that the vital statistics of an area can serve only as a crude index for comparison with other areas and that the value of such an index decreases greatly when the areas studied have different cultures or when one suffers the disorganization imposed by hard times, by famine, or by war.

These difficulties on the diagnostic side occur also on the nutritional side. Comparative

nutritional surveys range from estimates based on the food balance sheets of 2 nations to carefully measured intakes of individuals. A national balance sheet includes estimated domestic production, plus imports, less exports, and allowances for carry-overs of food stocks. Estimates must then be made of grain used for seed or animal feed, of edible crops used industrially (potatoes or grain for alcohol, fats and oils for paint, soap, etc.) and of wastage and spoilage. Finally, the food consumption can be estimated by distributing net residual food through the population by age groups, making allowance, if possible, for differences in food customs between different parts of the country, such as the home use of corn in the southern and of wheat in the northern United States. It is obvious that such estimates may indicate trends in single countries or demonstrate wide differences in the adequacy of the diets available, but that they have little application to small groups, especially if the differences are small.

The problem is exemplified in a study of individual food balance carried out by the Medical Nutrition Laboratory in U. S. Army messes.[17] The master menu called for the purchase of 3,900 calories daily per man, but the food offered in the mess hall measured from 3,068 to 3,326 calories daily per man. The cooking of bacon was one reason for the disappearance in calories; it involved a loss of 39 per cent of the original weight as drippings with a loss of 1,600 calories per pound of bacon used. Of the 182 Gm. of potentially edible fat available daily to each man only 134 Gm. were actually consumed. Thus not only national balance sheets can be deceiving but even estimates made under closely supervised conditions as in the U. S. Army messes. Evidently purchase and inventory records do not accurately indicate the true value of the food consumed.

Keys and Anderson[18] have attempted to circumvent these difficulties by personal estimates of diet consumption and of the incidence of coronary atherosclerosis in many parts of the world, supplemented in some studies by autopsy data. Reference will be made to some of these studies below. They concluded that, in general, there is indeed an association between total fat intake and the incidence of deaths attributed to arteriosclerotic heart disease. In Minnesota, Sweden, and Denmark, and high-income groups in Spain and Italy, they reported a high fat intake and a high incidence of coronary vascular disease. In the poor of these 2 countries, and in Japan, where the fat intake was low, they reported low incidence of coronary vascular disease. If the data can be confirmed, the trend of the findings is unquestionably significant. That the dietary factor, i.e., fat intake, rather than the genetic factor is possibly the more significant variable is indicated by comparisons of southern Japanese in Kyushu with their relatives in Hawaii[19] and of southern Italians living in Boston with those living in Naples. It must be borne in mind that there is a difference in the collection of the vital statistics in the areas under comparison that may vitiate these conclusions. The validation of vital statistics in these studies by inspection of hospital records and examination of groups of patients may not be as cogent as it would seem at first glance because standards for seeking hospital admission vary widely with cultural and social levels.

That the genetic factor may influence results of such studies is indicated by a recent cooperative study made by the life insurance companies in the United States. They investigated 18,000 insured lives for periods of up to 15 years and showed conclusively that persons who had reported 2 or more cases of early cardiovascular renal disease in their families were subject to death rates from cardiovascular disease that were from 1¾ to 2½ times those prevailing among all persons insured at standard premium rates.* More recently, Epstein et al.[20] have reported a study among garment workers which indicated that serum cholesterol and body weight, as well as blood pressure, were determinants in the incidence of coronary heart disease in men of Italian but not in those of Jewish origin.

Thomas[21] has reported recently on the incidence of acute fatal myocardial infarction in about 17,000 autopsies that were performed between 1910 and 1954. A change has occurred

* Impairment Study, 1951, Society of Actuaries, April 1954.

in the relative incidence of the disease in white individuals of the 2 sexes from 2:1 (males:females) before 1940 to 1:1 since 1940. This is thought to be due primarily to the greater increase of fatal infarction in elderly females. They also reported that the over-all incidence of fatal infarction was 5 times as high among the whites as among Negroes. This difference was greater in the period 1940 to 1954 than in the period 1910 to 1939 because the incidence among white individuals had risen greatly but that among Negroes had risen only slightly.

Clinical Approach

This approach depends primarily upon the association of increased incidence of atherosclerosis and of coronary arterial disease with certain diseases such as diabetes, myxedema, nephrosis, and xanthomatosis, when associated with hyperlipemia and hypercholesterolemia. This experience indicates that the equation of atherosclerosis with hypercholesterolemia is presumably valid, but does not establish the association between fat intake and hypercholesterolemia. Thus, Page and Farr[22] found no effect of high or moderately low-fat diets on plasma lipids of nephrotic children in short time experiments, and Mann[23] found no significant increases in serum cholesterol or β-lipoprotein in 2 normal young men fed high fat diets. On the other hand, some hypertensive patients exhibit large increase in both, while others show little or none.[1] The wide variation in individual response deserves much more attention. Turning to normal populations, the evidence is not concordant. Women in Iowa and Nebraska eat high-fat diets, but have a mean serum cholesterol of only 209 mg. per 100 ml.[24] On the other hand, Mayer et al.[25] found that high-fat animal or vegetable diets increased and low-fat diets decreased serum cholesterol of normal subjects, confirming earlier data of Keys.[26]

Cholesterol

Many years ago the clinical association between hypercholesterolemia and atherosclerosis was correlated with the finding that rabbits fed cholesterol in oil developed atherosclerosis. Cholesterol, once regarded as a nonmetabolizable building block in animal tissues and then as the mother of hormones, became to many the villain underlying arterial catastrophe. A large factor in this association—but biologically the least significant—was that the Liebermann-Burchard reaction made measurement of serum cholesterol easier than measurement of other lipids. In fact, the reaction may have dragged a blue-green herring across the trail of investigation by concentrating too much attention on cholesterol at the expense of substances of equal or greater potential interest.

The concentrations of plasma lipids usually tend to vary simultaneously in the same direction[27] and any one of them might be as significant as cholesterol. In man, it seems likely that serum cholesterol concentration is virtually independent of the intake.[28] But this cannot be stated firmly as a generalization. Thus "pure" vegetarians with low-cholesterol intakes tend to have lower serum cholesterol concentrations than nonvegetarians.[29] A problem of absorption also may be involved, since egg yolks added to the normal diet increase serum cholesterol concentration more effectively than pure cholesterol in a majority of normal subjects.[30]

Apart from the possibility that cholesterol may not play a dominant or specific role in atherosclerosis, determinations of serum cholesterol began to go out of fashion after the first of a series of reports by Gofman and his associates.[31] They found a close association between coronary atherosclerosis as manifested by myocardial infarction and subsequent serum concentrations of certain low-density lipoproteins; the association with over-all serum cholesterol content was not so close. These observations initiated a vast study, the results of which recently have been reported.[32] Unfortunately, the interpretations of the data are to some extent contradictory. The majority opinion holds that as an index the total serum cholesterol is as good as, if not better than, the low-density lipoproteins. The Gofman group continues to emphasize the clinical significance of the low-density, in their view atherogenic, lipoprotein molecules as compared to serum cholesterol. There are wide areas of agreement. Both serum cholesterol and low-density lipoproteins were found to have a statistical correla-

tion with each other, based primarily on the fact that the β-lipoproteins of lower S_f value are cholesterol-rich. Both also correlated with the incidence of myocardial infarction. It was concluded further that neither the analysis of one or both has specific predictive application for any one individual. It seems that comparative cost and complexity make it likely that serum cholesterol will remain the most used clinical guide to hyperlipoproteinemia and that chemical, ultracentrifugal, or electrophoretic determinations of serum lipoproteins will be used primarily in research. The need for both determinations is exemplified by the occasional dissociations between the 2 measurements.

Such were found in rural Central Americans[33] and in Nigerians,[34] both groups having low levels of cholesterol but definitely elevated levels of low-density serum lipoproteins.

Analytic methods for cholesterol must be rigidly standardized before data from different laboratories can be compared accurately. Due regard must be paid to such factors as day-to-day variability and variations between individuals in any "therapeutic" trials. It must be decided soon whether the North American "normal" mean is biologically a useful value. Lastly, before assuming that cholesterol intake is of no significance, it can be pointed out that in animals it is the feeding of fat and cholesterol together that provokes atherosclerosis. Feeding fat alone is comparatively, but not absolutely, ineffective. The significance of serum cholesterol concentrations in excess of the normal American range is illustrated in the Framingham study. In that study hypercholesterolemia, not necessarily from the diet, was associated with a 3-fold increased incidence of coronary artery disease.[35]

Fat

Total Fat Intake. Perhaps total fat consumption is more relevant to clinical atherogenesis than the intake of cholesterol. Keys, in particular, has placed emphasis on the proportion of total dietary calories contributed by the common food fats. His thesis is that changes in this proportion "result in corresponding changes in serum cholesterol concentration, even when the intake of calories, cholesterol, protein, and vitamins is constant."[35]

Certainly there is an abundance of data, both clinical and experimental, that tends to relate excess fat intake to atherosclerosis. Unfortunately, other significant parameters, such as total caloric intake, relative rate of caloric expenditure, and true obesity and exercise, are not easily disentangled from the problem of excess fat intake, so that this attractive hypothesis finds opposition in some quarters. With regard to the often-cited Norwegian experience, Morris[36] notes that mortality from cardiovascular disease is not easily estimated from the Norwegian vital statistics. Apparent mortality from this cause tended to decrease *before* the food shortages of World War II became severe, and this decrease was associated with declines in rates for dental caries, tonsillar hypertrophy, maternal mortality, suicide, and schizophrenia. He notes that in Britain, cardiovascular mortality decreased at the beginning of the war in 1939 (fat rationing began in 1940) but resumed a climbing trend in 1943, in spite of the fact that fat restriction continued and even intensified in 1947. He goes on to suggest that there may be "several causes and mechanism . . . involved in the human disease, some of them not related in simple fashion to serum cholesterol . . . but [that] it is a fallacy to consider that this automatically renders them unimportant."

There has indeed been a tendency to gloss over data that would run counter to the proposition that high-fat intake, plus hypercholesterolemia, results in atherosclerosis. Thus, Wilkinson, Blecha, and Reiner[37] found no relationship between diet and blood cholesterol and Shaffer[38] could not detect an increased incidence of coronary atherosclerosis among men on "ulcer" diets of milk and cream. In contrast is the association between fat intake and cholesterolemia demonstrated in normal subjects.[39] This last study was applied quickly by Morrison[40] to patients who had had myocardial infarcts. From the results of an 8-year survey, Morrison claimed increased survival (28 of 50 patients) among patients on a low-fat diet as compared with controls (12 of 50 patients) on a normal diet.

The Kempner rice diet is a good example of the effect of fat restriction. During the first months when there is usually a marked loss in weight, patients consuming this diet show considerable decreases in concentration of serum cholesterol. This is most evident when the initial cholesterol level is high.[41, 42] Watkins et al.[43] found that this dietary regimen brought about an average decrease of 40 mg. per 100 ml. of total cholesterol, involving 5 mg. of free and 35 mg. of ester cholesterol. The disproportionately large decrease in ester cholesterol confirmed Starke's observations[42] and was associated with decreased cholesterol-to-phospholipid ratio and with decreased serum neutral fats. This raised the question of possible hepatic dysfunction, perhaps imposed by the low-protein character of the diet. That the decisive factor was not protein lack was suggested by the fact that addition of small amounts of a vegetable oil to the diet of 5 patients and the feeding of 10 Gm. of oleic acid daily to 2 others restored the proportion of free-ester cholesterol and the other serum lipid abnormalities to normal *without* increasing serum cholesterol.

Mann et al.[44] have shown a rather striking effect of severe exercise in regulating levels of serum lipoproteins and cholesterol in young adult males who consumed a diet high in fat, both in total (153–174 Gm.) and in animal fats, with a daily caloric intake of approximately 6,000. The serum lipids were not increased as long as their caloric expenditure was great enough to prevent any appreciable weight gain. As soon as forced exercise was stopped, there was a gain in weight and an increase in level of serum lipids. In contrast to these findings, Keys et al.[45] as part of their epidemiologic studies, have estimated the physical activity of the groups of men they have studied in the several countries and have concluded that "differences in physical activity do not explain the large differences in serum cholesterol which are found when groups with different dietary habits are compared."

The problem of total fat intake, of the effect of moderate restriction of ordinary fats, and of the effect of exercise on the level of serum cholesterol must all be considered unresolved.

Animal vs. Vegetable Fat. The possibility that the kind rather than the amount of fat in the diet is responsible for atherogenesis has been raised. The first area of such studies has been a comparison of effects of animal fats with those of vegetable fats.

Some of the relevant data come from studies of vegetarians. In one study, serum cholesterol levels were higher in nonvegetarians than in lacto-ovo-vegetarians and "pure" vegetarians. The lowest concentrations of cholesterol were found in the "pure" vegetarians, in spite of the fact that 35 per cent of their total calories came from fat.[29] Somewhat comparable are the data that compare male adult mean serum cholesterol concentrations among Peruvian Indians, Navaho Indians, American Trappist monks, and Cleveland Americans.[46] The respective levels were 186 $\pm$ 11.8, 175 $\pm$ 6.2, 184 $\pm$ 14.9, and 229.7 $\pm$ 4.4. In all 3 special groups there were lower serum cholesterol concentrations than in the Cleveland group although the Navaho Indians may be somewhat low partly because they were in the hospital.[47] The Peruvian diet was largely vegetarian. The diet of the Trappist monks was lacto-ovo-vegetarian and relatively low in calories, 1,600 daily, (protein 51, fat 34, carbohydrate 275). Reports on the Navaho diets show that they consume a not inconsiderable amount of fat and cholesterol, but that there is uncertainty as to the exact composition of the diet, particularly in places well removed from the hospitals.[48]

The possible association between vegetarianism and low levels of serum cholesterol is also tested by the data from a study of Eskimos, who eat a high-meat, high-fat diet. With a procedure that yielded a mean value of 177 mg. per 100 ml. total serum cholesterol for the control group of Canadians, the mean in 27 Eskimos was found to be 141 (range 93–222) and in 6 Devon Island Eskimos—presumably consuming less than the others of cereal fare—132 mg. (range 116–158). The fats consumed were largely of marine origin, and, like vegetable fat, relatively unsaturated. However, tuberculosis is common among Eskimos and may account for the relative lipopemia.[49]

Unsaturated Fats. The reported effects of

vegetable fats may be a function of their degree of unsaturation or of their content of "essential fatty acids." The parameter of saturation of fat as a significant factor in cholesterolemia and, by extension, in atherosclerosis, recently has been explored in human beings by Kinsell,[50] Ahrens,[51] Beveridge,[52] and Bronte-Stewart.[53] These experiments showed that relatively unsaturated fats of vegetable or marine origin tend to lower while, per contra, the particular hydrogenated vegetable fats usually, and saturated animal fat rather regularly, tended to increase serum cholesterol.

It is important to keep in mind that the "test conditions" (variously, formula diets, tube feeding, grossly distorted diets, hospitalized patients, medical students, poor Bantus) do not necessarily bear directly on the possible effects of addition of reasonable amounts of unsaturated fat to a North American "meat and potatoes" diet, and, at present, cannot be extrapolated to the normal diets of large groups of people free of cardiovascular disease. It is, of course, only possible to obtain the evidence on which to base a way of dietary life where such strictly controlled investigative conditions can be imposed. This is still an area of clinical investigation. It is reasonable to assume that none of the dietary regimens studied will be of practical value, as such, to people who are in good health. Some of the diets contained as much as 40 to 60 per cent oil or fat by weight. The bizarre character of some of these diets is exemplified by one that included 100 Gm. of pilchard oil daily (iodine number 180). This was found to counter the hypercholesterolemic effect of concurrently consuming 10 eggs daily. This observation was made with 2 cooperative Bantu subjects and for periods of only a few days. Nonetheless, this preliminary evidence has provided an important investigative area that is now under intensive study.

The mechanism by which unsaturated fats might counter lipemia and hypercholesterolemia is not understood. Beveridge, Connell, and Mayer[54] are less concerned with the degree of saturation than with as yet unidentified cholesterol-increasing and cholesterol-depressing factors found respectively in animal and vegetable fat.

Speculative hypotheses, like those of Sinclair[55] and Schroeder[56] have been formulated. The starting point of this type of hypothesis is that cholesterol is normally esterified with unsaturated fatty acids. When these are unavailable, cholesterol esterifies with saturated fatty acids provided by the dietary fats or synthesized in the body from carbohydrates. The hypothesis states that it is these saturated cholesterol esters which tend to be deposited in the arterial intima. Inability to form arachidonic from linoleic acid (2 essential fatty acids) may be involved, and this latter synthesis may depend on pyridoxine. Therefore, pyridoxine deficiency might have the same effect as a deficiency of unsaturated fatty acid. It is also suggested that cholesterol excess might have similar effect. On this basis, hypercholesterolemia and atherosclerosis would be attributable to absolute or relative deficiency of unsaturated fatty acids. Sinclair's estimates of the composition of western European diets led him to conclude that they are indeed marginally deficient in unsaturated fatty acids, but more recent evidence does not support this estimate. Lack of essential fatty acids now seems an unlikely factor in atherogenesis. Schroeder's speculation is that trace metals contaminating prepared foods might poison the pyridoxal enzyme systems and lead to atherosclerosis in people whose diets are rich in saturated fat and cholesterol. Again, there is no substantial evidence in favor of this view.

Both series of propositions are highly speculative. It would be premature to act on these assumptions without good evidence for their validity. The fact is that the basic problem is not only lipemia, hypercholesterolemia, or the loading of the liver with lipid, but it is atheromatosis, and, in particular, myocardial infarction or cerebral thrombosis. Atheromata have not been described or associated clinically or experimentally with fatty acid deficiency. Further, myocardial infarction is not generally precipitated in animals by excessive intake of any particular fat or of cholesterol, or by a deficiency of pyridoxine or any unsaturated fatty acid. Incompletely reported experiments of Hartroft, however, suggest that in rats on special diets this may be possible.

Other observations of interest include those of Curran,[57] who has evidence that cholesterol esters of rabbits fed saturated fats hydrolyze less rapidly *in vitro* than the cholesterol esters of animals given unsaturated fats. This suggests that the latter esters may be less stable and perhaps more easily metabolized *in vivo*. This view could easily be tested on the large series of cholesterol esters synthesized by Page and Rudy.[58] Very low fat diets increase hepatic and decrease plasma cholesterol in rats.[57] Absence of essential fatty acids may be the result of failure of cholesterol esters containing other than polyunsaturated acids to be available for proper metabolism. In monkeys[6] increasing amounts of corn oil caused serum cholesterol to rise progressively; hydrogenated cottonseed oil at low, medium, or high levels, caused even greater rises in serum cholesterol, while native cottonseed oil gave responses similar to corn oil; the responses to lard resembled those obtained with the hydrogenated cottonseed oil. That the changes in serum lipid may not reflect the tissue fat pool is shown by measuring hepatic, as well as serum cholesterol in rats fed an unsaturated oil (soya bean oil) and one more saturated (coconut oil): on these rations, hepatic cholesterol was more than doubled in rats receiving the unsaturated oil as compared with their controls fed saturated fats. There was a tendency to low serum cholesterol concentration in the rats with the high levels of hepatic cholesterol.[60] Saturation, as such, is not the only factor. Thus, rats were given a variety of fats with added cholesterol and cholic acid.[61] They were sacrificed at 8 and 12 weeks and the serum cholesterol mean values were averaged. Those rats given coconut oil and butter respectively showed mean serum cholesterol levels of 553 and 453 mg. per 100 ml.; those given cottonseed and corn oils had lower cholesterol levels, namely 308 and 392 mg. per 100 ml.; hydrogenated cottonseed oil with two thirds the iodine number of the raw oil yielded a mean of 461 mg. per 100 ml. Tung oil, which is highly unsaturated, yielded the highest mean serum cholesterol, namely 1130 mg. per 100 ml. The fact that tung oil is rich in eleostearic acid, an octadecatrienoic acid and an isomer of linolenic acid, which is uncharacteristic of animal tissue, may bear on this unanticipated result. The amount of sudanophilic material under the endothelium of the valvular endocardium and aorta was estimated and with all oils was found to be proportional to the level of serum cholesterol. Thus, if this sudanophilic material is indicative of early "atherogenic activity," it would appear to be mirrored by the level of serum cholesterol.

It has been suggested that the spacing of fat meals is important. Certainly, in hyperlipemia and many of the secondary lipemias, blood lipids can be maintained at "normal" level by properly spacing fat without reducing the total daily intake.[62]

Fat and Clotting. The hypothetical sequence in vogue since the time of Virchow from hypercholesterolemia to increased intimal lipid deposition ending in atheroma has been questioned. Duguid has restated the Rokitansky concept that atheroma begins in deposition of fibrin and extends by incorporation and organization of these deposits.[63, 64] The bridge between this view and that which associates atherogenesis with lipemia is provided by experiments showing that lipemic blood may hasten coagulation *in vitro*[65-67] or shorten plasma clotting time induced by an incomplete thromboplastin.[68] Increase in coagulability of lipemic plasma does not seem to be found by all observers.[69] The effect of fat ingestion on coagulation is possibly associated with changes in circulating phosphatidyl-ethanolamine,[66, 70] which may act as a thromboplastin. Fibrinolysis appears to be inhibited by alimentary lipemia, among other things.[71] These associations are of considerable interest, since they tend to link atheroma and lipemia with thrombosis. They are preliminary. In particular, the concept of atherogenesis on the basis of fibrin deposition has little, if any, direct or sequential demonstration.

Carbohydrate

The conversion of carbohydrate to saturated and mono-unsaturated fatty acid is implicit in the "corn-hog ratio," which dictates a portion of the farm economy. Further, ingestion of a high carbohydrate diet usually implies a low-fat ration and vice versa. But there may

be still subtler influences of carbohydrate feeding. Thus, in rats, the kind of carbohydrate fed seems to affect the catabolism of cholesterol to bile acid.[72] Chow-fed rats excreted more bile acid than rats fed sucrose as the primary carbohydrate source. When a variety of purified carbohydrates was studied, it was shown that starch elicits a larger bile acid output than the simple sugars. When cholesterol was added to the diet, rats given starch had lower levels of serum cholesterol than rats fed simple sugars. In man it has been shown that the total blood lipids of Chinese, who consume only 10 per cent of their calories as fat and 90 per cent from carbohydrate and protein, are higher than comparable groups of Americans, who consume 43 per cent of their calories from fat.[87]

Proteins

Dietary proteins also may be involved in experimental atherosclerosis. The production of atherosclerosis in the monkey was accomplished by means of diets containing a protein prepared from soybeans and commonly referred to as "alpha protein" and prevented when casein was the dietary protein.[7] This effect of alpha protein is presumable due to its low sulfur acid content, but this supposition has not been rigorously proved. Similar results have been obtained in rats.[73] Other studies with rats[74] showed that the hypercholesteremic response varied according to the protein level. The lowest response was observed among those animals receiving the highest level of dietary protein. Since atherosclerosis in man is associated with an abundant diet, it is difficult to believe that diets low in protein or low in essential amino acids can be a causative factor. Possible interrelations between fat and protein intakes are unexplored. In any event, these are indications that cannot be completely ignored.

American Diet

Has there been a marked change in the American diet during the past one or two generations—a period in which the incidence of coronary heart disease and atherosclerosis may have increased? What are the principal changes, and do they involve the amount and type of fat?

Katz et al.[75] stated unequivocally that the fat content of the American diet has increased. To prove his point, he cited data from the Department of Agriculture going back to 1910. But these data are of food estimated to be available at the retail level and are really no true measure of the actual food consumed. Stare[76] was not nearly so certain that there has been any marked increase in the fat content of American diets. He pointed out that data on food consumption for estimates of dietary changes are generally obtained by 2 methods: the official tables of food availability prepared by the Department of Agriculture, and survey data of families or particular groups. The first method, that of food availability, erroneously called food-consumption data, consists of estimates of food stuffs available for civilian consumption based on foods at the retail level. The data have not been adjusted for waste in homes or wastes in institutions. Data on waste are usually not very reliable; however, quantity of waste is probably very important. For example, how much fat is discarded after the cooking of meats, bacon, or fat frying? Have not the cooking methods changed in this country so that more food is broiled and excess fat discarded? Since in periods of prosperity waste may be greater than in periods of austerity, food-availability tables may not present a true picture of changes in the dietary. The tremendous fat collection from kitchen waste during the war years is an indication of the degree of the loss.

From the data of the Department of Agriculture[77] it is found that from 1935 to 1955, the average caloric consumption per capita per day has decreased slightly, approximately 70 calories. Protein has increased from 90 to 97 Gm., fat from 134 to 148 Gm., and carbohydrates have decreased from 440 to 384 Gm. per day. The decreased use of potatoes and cereals, and an increase in milk, meat, and eggs seem to have been responsible for these changes. Since consumption of cereals and potatoes has decreased, as well as total calories, the *percentage* of fat in the diet would show an increase even if the total fat consumed has not changed.

The second method of estimating food consumption is the dietary survey. Many studies, ranging from approximately 1900 to the present day, show a considerable variation in dietary intake, depending on the group and area under scrutiny. However, variations with time are not very striking. For example, a dietary survey of college men in a "boarding club" in 1891 showed 44 per cent of the calories coming from fat, and a survey of women eating at college clubs in 1894 reported 36 per cent of the calories came from fat.[78] And even the Harvard Crew in 1898 consumed a diet providing 39 per cent of the calories as fat.[79] A study in 1953 of adult women showed the percentage of calories derived from fat ranged from 36 to 46 per cent of the total.[80] Thus, there may not have been an increase in fat consumption by Americans over the past 50 years as claimed by some. A study of the U. S. Army rations in the western outpost in the late 1880's showed a fat content almost identical with current U. S. Army rations.[81] This lack of change in American dietary can be correlated with the stand taken by the few that there has been no real increase in coronary heart disease, but only an increasing awareness.

It is true that the use of hydrogenated fats has increased in the past 50 years, but since the 1920's there has been no major increase until after the war (about 1945), when the use of margarine went up sharply. Hydrogenation is a controllable process and within limits the relative amounts of mono-unsaturated and poly-unsaturated fatty acids can be varied. As hydrogenation is practiced commercially, it is not carried to complete saturation. On the contrary, considerable amounts of unsaturated fatty acids remain, including essential fatty acids.

Actually, the proportion of animal and vegetable fats in the diet has remained relatively constant. Again, from Department of Agriculture tables, of 132 Gm. of fat available for human consumption in 1935 to 1939, 73 per cent was from animal sources and 27 per cent from vegetable fats. In the 1955 preliminary report[82] 158 Gm. of fat were available, 70 per cent animal, and 30 per cent vegetable fat—very little change.

It may be of interest to mention that early margarines in this country were made partly from beef fat, though for many years hydrogenated vegetable fats have been used almost exclusively. Margarine in other countries is made from various types of fats, whale oil being used extensively in the United Kingdom.[83] Interestingly, per capita availability of lard is about the same now as it was in 1910[77] but lard processing now includes refining, decolorization, and often the addition of some amounts of hydrogenated fat (also, in some cases, addition of gum guaiac and various anti-oxidants).[84]

It might be pointed out that an increase in the consumption of hydrogenated fats during the past 25 to 30 years does not necessarily mean a decrease in the intake of the essential fatty acids. This follows from a number of reasons.

1. While the use of hydrogenated vegetable oils has increased over the past several years, these fats are substitutes for lard and butter and hence their use has increased slightly the amounts of essential fatty acids in the diet. While it is true that hydrogenation gives rise to a variable mixture of isomers, there is no evidence that those isomers act as anti-linoleic compounds, particularly with regard to cholesterolemia. In fact, there is evidence[84] that the linoleic acid in fats treated by selective hydrogenation has biologic activity and is at a level as high as 13 per cent and usually not less than 10 per cent. In addition the use of these same oils in their natural state has increased and has led to a substantial contribution of essential unsaturated fatty acids.

2. Gross measurements of changes of saturation induced by hydrogenation and frequently evaluated by determination of iodine number do not necessarily indicate the degree of change in the content of biologically active poly-unsaturated acids. During hydrogenation, the content of normal linoleate of an oil, while reduced, is not abolished.

McCann and Trulson[85] have recently estimated the intake of essential fatty acids in current and past American diets. They comment as follows: "However, there has been no marked change in the total amount of essential unsaturated fatty acids in the American diet

over the past half century. The increased saturation of fats induced by the hydrogenation of shortenings and margarines has been balanced by an increased consumption of 'other fats and oils,' fats which are mostly unsaturated and have a high content of essential fatty acids." The increased consumption of other fats and oils has not increased the *total* fat intake because of decrease of butter, lard, bacon, and trimming off the fats of meats.

General Comment

One can summarize the hypotheses presented as follows: (1) that diet may play an important role in the pathogenesis of atherosclerosis, (2) that the fat content and the total calories in the diet are probably important factors, (3) that it may be more the type of fat than the total fat, or the ratio or balance between the saturated and certain unsaturated fats that is the basic determinant, and (4) that the proposition that the character of the American diet has so changed during the past 50 years as to increase the incidence of coronary vascular disease cannot be supported. It was indicated that (5) other aspects of fat metabolism may be determinants, and (6) that a wide variety of other factors, dietary and nondietary, may be of equal or greater importance, and (7) that infarction, the real nub of the problem, is not generally produced experimentally, despite the extensive and severe atherosclerosis that has been produced. Possibly this objection has been very recently overcome.

It should be realized that these conclusions are subject to some very basic criticism. One is that most of the studies have focused attention on the concentrations of serum cholesterol, serum lipid, or serum lipoprotein without proper emphasis on the focus of the problem, which is atheroma and infarction, whether myocardial or cerebral. Is there compelling evidence that, if we treat the hypercholesterolemia by dietary means, we are doing anything to lessen the chances of myocardial infarction? Perhaps the best that can be said is that there is an association that has statistical value, but that is not an obligatory association either in small groups or, and much less so, in an individual.

Even if one accepts the equation *hypercholesterolemia = atherosclerosis* (or some variant thereof) the fact that serum lipid concentrations, perhaps more in some people than in others, show considerable "spontaneous" fluctuations makes its application difficult. Variations of serum lipid concentrations among individuals of the same sex and age, consuming similar diets, are also great. Consequently, data based on single determinations are potentially highly inaccurate, and control data, by repeated observation on standard regimes, should be secured over several weeks.

Vital statistics, particularly from countries with different methods of reporting, understaffed health departments, and low autopsy rates, are very likely to be misleading. The diagnostic accuracy of all physicians is not equal, standards vary from place to place. The taking of diet histories is time consuming and, at best, yields data of only moderate accuracy. When obtained through interpreters, under the press of time and when good rapport has not been possible, diet histories lose even this limited value. A national diet low in fat is usually also low in sucrose and animal protein; it is usually high in fiber and starch, and the vitamin and mineral content may differ from American diets.

Lastly, there are other common factors in human life that are atherogenic, but not related to lipemia. Of these, the most common and best documented is arterial hypertension. This association is well recognized. The greatest frequency of complications of atherosclerosis, fatal and nonfatal, was found in the group of patients whose severe hypertensive disease had been brought under some control with antipressor drugs. Among these, such complications occurred 3 times as often in those with high (greater than 110 mm. Hg) diastolic pressures than in those with lower average pressure. In these patients, there was no demonstrable association between the incidence of these complications and the level of serum cholesterol or of the light or dense lipoprotein fractions.[86]

Conclusion

Atherosclerosis, cerebral thrombosis, and myocardial infarction are diseases in which

numerous factors are involved. Diet and nutrition are important factors in experimental atherosclerosis and, very probably, in the human disease. Thrombosis and infarction of the cerebral, cardiac, and renal vessels occur in severely sclerosed arteries, but so far neither has been clearly produced experimentally.

Evidence is presented to suggest a possible general association with high fat consumption, but it is difficult to disentangle this from caloric balance, exercise, changes in body weight, and other metabolic and dietary factors that may be involved. Thus, the evidence at present does not convey any specific implications for drastic dietary changes, specifically in the quantity or type of fat in the diet of the general population, on the premise that such changes will definitely lessen the incidence of coronary or cerebral artery disease. On the other hand, the fact that obesity is a nutritional failure, that it is caused by consuming more energy than one expends, that dietary fats are the most concentrated source of energy, providing some 40 to 45 per cent of the daily caloric intake, suggests that many should consume less calories. For most, this will mean eating less fat.

Prudence, as well as habit and taste, will dictate the selection of a diet with some fat. Diets providing 25 to 30 per cent of the calories from fat, rather than the current 40 to 45 per cent in the American diet, can still provide palatable meals for our accustomed tastes.

The key points of nutritional common sense for better health generally, and most likely in regard to atherosclerosis specifically, consist of a balanced, varied diet that adjusts total calories to reach or maintain a desirable weight. Such a diet should provide more protein from lean meat, fish, poultry, and animal products, cereal and grain products, and a reasonable selection of fruits and vegetables. The fat content should be sufficient only to meet caloric and essential fatty acid demands.

These conclusions obviously apply to the general population, and not to patients or to individuals with a strong family history of early deaths from cardiovascular disease, who are being observed with some regularity by their physician. Here, the newer concepts of nutrition readily suggest various types of diet therapy that may prove useful to certain patients. Investigative procedures of this type, together with continued basic research, will, in time, provide the facts upon which sound dietary recommendations may be made to the public at large and which may help in lessening the prevalence of cerebral and coronary disease with consequent stroke and myocardial infarction.

Summario in Interlingua

Atherosclerosis, thrombosis cerebral, e infarcimento myocardial es morbos in que un grande numero de factores es implicate. Dieta e nutrition es factores de alte importantia in atherosclerosis experimental e probabilissimemente etiam in le occurrentia del morbo in humanos. Thrombosis e infarcimento del vasos cerebral, cardiac, e renal occurre in arterias que es severmente sclerotic, sed usque al tempore presente ni le un ni le altere ha essite reproducite clarmente per medios experimental.

Es presentate datos que supporta le vista que il existe un association general con alte grados de consumption de grassia, sed il es difficile isolar iste factor ab le balancia caloric, le intensitate de exercitios, alterationes del peso corporee, e altere factores metabolic e dietari que es possibilemente interessate in le problema. Assi, le datos nunc disponibile non justifica le recommendation de drastic modificationes dietari—specificamente con respecto al quantitate o al typo de grassia in le dieta del population general—con le expectation que tal modificationes va definitemente reducer le incidentia de morbo de arteria cerebral o coronari. Del altere latere, le facto que obesitate es un dysfunction nutritional, que illo resulta del consumption de un excesso de energia in comparation con le expension de energia, e que grassias dietari (que provide 40 a 45 pro cento del diurne ingestion caloric) es le plus concentrate fonte de energia supporta le recommendation que multe personas deberea reducer lor consumption de calorias. In le majoritate del casos isto significa un reduction del consumption de grassia.

Prudentia insimul con habitude e preferentia personal va determinar le selection de un dieta

con un certe portion de grassia. Dietas que deriva 25 a 30 pro cento de lor contento caloric ab grassias (in loco del 40 a 45 pro cento in le dieta american currente) es certo capace a provider repastos appetibile secundo nostre gustos habitual.

Le punctos cardinal in un programma dietari de senso commun—tanto in le interesse de un meliorate stato de sanitate physic in general como etiam con respecto a atherosclerosis in particular—es recommendationes visante a un balanciate e variate dieta que subordina le total caloric al objectivo de attinger o mantener un peso desirabile. Un dieta de iste genere proviserea plus proteina ab carne magre, pisces, volatiles, cereales, e productos animal e cereal insimul con un selection adequate de fructos e vegetales. Le contento de grassia debe sufficer solmente a satisfacer le requirimentos caloric e le requirimentos de acido grasse essential.

Il es obvie que iste conclusiones vale pro le population general e non pro patientes o pro individuos con pronunciate historias familial de morte prematur ab morbo cardiovascular, le quales es sub le observation plus o minus regular de lor medicos. Pro tal personas, le plus recente conceptos nutritional suggere varie typos de therapia dietari que va possibilemente provar se benefic in casos specific. Investigationes del presente typo, insimul con continuate recercas fundamental, va establir in le curso del tempore le factos super le base del quales salubre recommendationes dietari pote esser facite al publico in general e ab le quales on pote expectar que illos va servir a reducer le prevalentia de morbo cerebral e coronari con consequente apoplexia e infarcimento myocardial.

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Reversible Cardiopulmonary Syndrome with Extreme Obesity

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A syndrome consisting of obesity, somnolence, cyanosis, periodic breathing, and polycythemia, with congestive heart failure has been observed in 6 patients. The effect of weight reduction and the mechanisms responsible for the symptoms and signs are discussed.

SIX obese patients have been observed during the past 3 years, with remarkably similar symptoms and findings. These consisted of somnolence, cyanosis, periodic breathing, polycythemia, rightward electric axis by electrocardiogram, and the clinical picture of congestive heart failure. The syndrome appears to be related to obesity and may be reversed by weight reduction. The present report outlines the features of the syndrome and offers a tentative explanation of its production.

Case Reports

Case 1 (E. F.)

A 50-year-old white housewife was admitted to Duke Hospital in May 1951, with dyspnea, orthopnea, and ankle edema, of 1 year's duration. She had been obese all of her life. At age 13 she weighed 193 pounds; at age 22 she reached 258 pounds. This weight was maintained until about age 37, when she was told she had hypertension, and was treated with diet, bed rest, and "thyroid tablets." She lost 50 pounds and her blood pressure was said to have become normal. However, she again began to gain weight, and 1 year before admission, when her symptoms began, she weighed 325 pounds. About 11 months prior to admission the patient was placed on a low-salt diet by her local physician with relief of dyspnea, orthopnea, and ankle edema. This improvement continued until about 3 months before admission, when symptoms recurred. At that time she also noted a blue tinge to her lips and nails. Marked somnolence had developed, and the patient's daughter described periods of alternate apnea and deep noisy respirations during sleep.

On admission the patient was in respiratory distress. Her weight was 364 pounds; her height was 64¼ inches. Blood pressure as measured by a standard cuff, was 150/90 mm. Hg; the respiratory rate was 28 per minute. There was cyanosis of the lips and nails. Rales at both lung bases, cardiomegaly, ascites, and moderate pitting edema of both legs were observed.

The red blood count was 6.75 million, the hemoglobin 19.0 Gm. and the hematocrit 61 volumes per cent. The white blood count was 8,800 with a normal differential count. The number of platelets on a stained smear was not increased. Urine examination revealed a specific gravity of 1.013, a trace of protein, and no sugar. A fasting blood sugar was 109 mg. and the blood cholesterol was 110 mg. per 100 ml. The basal metabolic rate was plus 36 per cent by the usual weight-height standards. An electrocardiogram revealed right axis deviation and T-wave abnormalities that were of uncertain significance (fig. 1).

The patient received digitoxin, mercurial diuretics, and a low-salt 800-calorie diet. Improvement in symptoms was prompt. Blood pressure fell to normotensive levels on the second hospital day, and remained there during the entire hospitalization. Inhalations of 100 per cent oxygen produced a reversal of her cyanosis to a normal pink color. As the patient lost edema fluid and weight, the red blood count, hemoglobin level, and hematocrit level gradually rose. One liter of blood was withdrawn during the latter part of her hospital stay. She lost 66 pounds of weight in 20 days and was remarkably improved symptomatically.

After discharge the patient was occasionally seen in the outpatient department. Her weight gradually fell to 208 pounds in March 1952. At this time her hemoglobin level was 13.5 Gm. and the hematocrit value was 46 volumes per cent. She was symptom free, and digitalis was discontinued. During the next 1½ years she again began to gain weight and was readmitted to Duke Hospital on August 21, 1953, at her own request for more intensive dietary restriction. At this time she weighed 234 pounds. There were no symptoms of congestive heart failure. Blood pressure was 120/85 mm. Hg. The lungs were normal, and there was no cardiomegaly. Hemoglobin level was 14.0 Gm., red blood count was 4.6 million, and the hematocrit reading was 45 volumes per cent. White blood count was 6,600. Urine examination revealed a specific gravity of 1.025, with no protein or sugar. An electrocardio-

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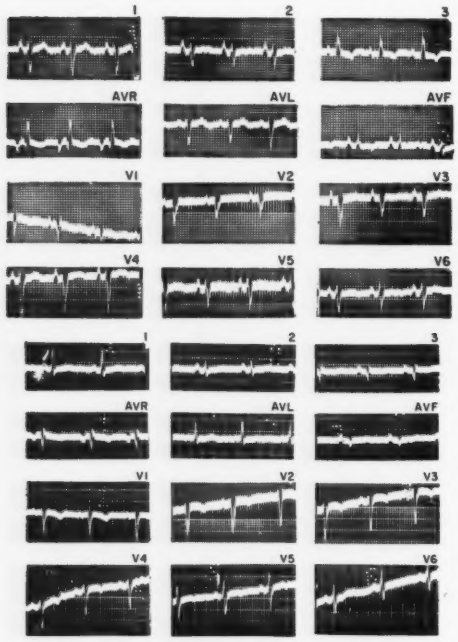

FIG. 1. *Top.* Electrocardiogram, case 1 (E. F.), before weight reduction. *Bottom.* After weight reduction.

gram showed a marked shift in electric axis in comparison with previous records. Left axis deviation was now present and T-wave inversion in the precordial leads suggested anterior wall ischemia (fig. 1). The patient was placed on a 600-calorie diet, plus added vitamins, and lost 16 pounds of weight during a 9-day hospitalization,

Since discharge the patient has been followed by her private physician. She has been unable to restrict calories sufficiently and her weight has stabilized at about 250 pounds. At this weight there has been no return of symptoms, cyanosis, or polycythemia. The blood pressure has remained between 130/90 and 150/100 mm. Hg. On her last follow-up report in June 1956, the patient was asymptomatic although still overweight.

Case 2 (J. D.)

A 39-year-old Negro mechanic was admitted to the Durham Veterans Administration Hospital in March 1954. He had noted exertional dyspnea for 4 months, orthopnea and paroxysmal nocturnal dyspnea for 3 months, ankle edema and abdominal swelling for 1 month. His usual weight had been 170 pounds. He had gained weight prior to onset of the above symptoms, and estimated his weight to be 200 pounds at the time of their appearance. Soon after exertional dyspnea was noted, he was seen by his physician, who administered mercurial diuretics with moderate relief of symptoms. The past history was unremarkable except for an episode of arthritis involving both feet and knees, 8 years previously. He recovered from this episode in 2 weeks, and had been symptom free until the onset of the above symptoms. He denied previous chest pain, hypertension, or renal disease.

On admission the patient was dyspneic and orthopneic. His weight was 257 pounds and his height was 63½ inches. The blood pressure was 140/120 mm. Hg, and the pulse was regular at 150 per minute. The fundi were normal. Bilateral basilar rales, cardiomegaly, a grade I apical systolic murmur, hepatomegaly, ascites, and marked lower extremity edema were present on admission.

The hemoglobin was 14.8 Gm., and the hematocrit value was 43 volumes per cent. The white blood count was 5,500, with a normal differential count. Urinalysis showed a specific gravity of 1.006, a faint trace of protein, and no sugar. The fasting blood sugar was 108 mg. and the nonprotein nitrogen was 38 mg. per cent. An electrocardiogram revealed a vertical electric axis, atrial flutter with 2:1 A-V block, and a ventricular rate of 150 per minute. Films of the chest showed marked cardiac enlargement that was thought to be chiefly left ventricular. Fluoroscopy revealed no atrial enlargement. Skull films were normal. Basal metabolic rate was plus 32 per cent.

On admission the patient was placed on a 1000-calorie, 200-mg. sodium diet, and a mercurial diuretic was administered. The patient lost 7 pounds during the first 24 hours. Symptomatic improvement was striking. The atrial flutter with 2:1 block remained unchanged for the first 4 hospital days; digitalization then increased the block to 4:1. Quinidine failed to abolish the atrial flutter.

With improvement in dyspnea and orthopnea in the first few days of hospitalization, the patient was noted to be extremely somnolent, falling asleep whenever left quiet for a few minutes. During these periods Cheyne-Stokes respirations were noted. On the third day of hospitalization, during cardiac catheterization, arterial oxygen saturation ranged from 51 to 78 per cent during the periodic breathing. Inhalations of 100 per cent oxygen for 15 minutes raised the arterial oxygen saturation from 78 to 99 per cent.

After 3 weeks of hospitalization the patient was allowed to return home for a 2-week leave of absence. During this period he stopped all medications and relaxed his dietary sodium restriction without change in his symptoms. Atrial flutter continued with a regular 4:1 block. He was then discharged on April 28, 1954, on a 1200-calorie low-salt diet, but with no digitalis or diuretics. He had lost 65 pounds during his hospitalization.

On a return visit his weight was 187 pounds.

He had noted no return of his original symptoms of congestive heart failure. Blood pressure was 140/100 mm. Hg, and the pulse rate varied between 60 and 100 per minute. The rhythm was irregular as the degree of A-V block shifted from 2:1 to 4:1. There were no signs of congestive heart failure.

The hemoglobin was 14.4 Gm., the hematocrit value 48 volumes per cent, and the white blood count 6,100. Urine analysis was negative except for a slight trace of protein. Arterial oxygen saturation was 93.5 per cent. Because of the arrhythmia he was digitalized and a regular 4:1 block resulted. He was discharged on June 7, 1954, having further reduced his weight to 177 pounds.

The patient was readmitted on April 11, 1955, for reevaluation of the cardiac status. His weight had increased to 206 pounds. He had continued to take digitalis, but had not followed his salt-free reduction diet. In spite of the weight gain and the dietary indiscretions, the patient felt well, with no recurrence of the original signs and symptoms of congestive heart failure. Blood pressure on admission was 160/120 mm. Hg. There was no somnolence or cyanosis. Cheyne-Stokes respirations again appeared when the patient slept. Mild cardiomegaly was seen on chest film. The hemoglobin was 15.2 Gm. with a hematocrit reading of 48 volumes per cent. Fasting blood sugar was 108 mg. per 100 ml. Glucose tolerance test was normal. Visual fields were normal. An electrocardiogram revealed normal sinus rhythm and a shift in electric position from a vertical position to a normal intermediate position. Arterial oxygen saturation ranged from 90 per cent to 93 per cent, rising to 100 per cent with inhalations of 100 per cent oxygen.

He was again placed on a low-sodium, 1000-calorie diet at the time of discharge. Since then he has remained free of symptoms, but has been unable to follow his diet. His weight had increased to 214 pounds on his last outpatient visit on November 10, 1955.

Though the onset of congestive failure in this patient may have been immediately precipitated by the development of the atrial flutter, this abnormality did not explain the arterial oxygen unsaturation, the somnolence, and other features. For this reason the case was regarded as a true example of the syndrome.

Case 3 (R. P.)

A 34-year-old white farmer was admitted to the Veterans Administration Hospital, Fayetteville, North Carolina, on October 18, 1954. He had been referred to that hospital because of signs and symptoms of congestive heart failure. The patient weighed 147 pounds in 1945 at the time of discharge from the Army. He had gradually gained weight up to a maximum of 300 pounds at the time of admission. Progressive exertional dyspnea had been present for 4 years, and ankle edema and orthopnea for 1 year. During that time he had received weekly mercurial diuretics from his local physician. On admission he was acutely dyspneic and plethoric. There was cyanosis of the lips and nail beds. Blood pressure was 104/70 mm. Hg. Moist rales were heard over both lung bases, and there was pitting edema of both feet and ankles.

Admission laboratory work was as follows: hemoglobin 18 Gm., hematocrit 63 volumes per cent, white blood count 10,600, with a normal differential count. Urine analysis was negative except for a trace of protein and 6 to 8 white blood cells per high-power field. Nonprotein nitrogen was 38 mg. per 100 ml. A chest film revealed cardiomegaly and prominence of the pulmonary arteries. An electrocardiogram showed a Q wave in lead III, and in V_1 to V_3. The QRS vector was extremely posteriorly directed, the QRS being predominantly down in all the V leads. These findings were of uncertain significance.

The patient was placed on an 800-calorie low-sodium diet and digitalized with digitoxin. He was maintained on 0.15 mg. of digitoxin daily and was given mercurial diuretics every 2 to 3 days. He lost 25 pounds in the first 3 weeks. His improvement in symptoms was dramatic.

To obtain more specialized studies the patient was transferred on November 19, 1954, to the Veterans Administration Hospital, Durham, North Carolina. At that time he was much improved symptomatically as compared to his state 3 weeks earlier. He complained only of dyspnea on unusual exertion; however, cyanosis was still present. His weight was 269 pounds. Blood pressure was 130/85 mm. Hg. Cheyne-Stokes respiration was noted during sleep. There were no signs of congestive heart failure except for a 1 plus pitting edema of the ankles. Heart size was difficult to evaluate because of the patient's obesity. There was no hepatomegaly or splenomegaly.

Laboratory studies were as follows: hemoglobin 19.3 Gm., hematocrit 60 volumes per cent. The cells were normochromic and normocytic. White blood count was 11,550, with a normal differential count. Platelet count was normal. Urine analysis revealed no abnormalities. Nonprotein nitrogen was 18 mg. and blood cholesterol was 210 mg. per 100 ml. Serum uric acid was elevated to 7.7 mg. per 100 ml. A bone marrow smear and iron turnover studies were normal. Visual fields and skull films were normal. Fluoroscopy of the chest revealed a transversely placed heart with no specific chamber enlargement. An electrocardiogram revealed a vertical electric axis. The T waves were inverted in V_1, V_2, and V_3, and were compatible with anterior wall ischemia.

Pulmonary function studies showed a reduced functional residual capacity and expiratory reserve. Cardiac catheterization studies revealed moderate elevation of pulmonary arterial pressure (mean =

25 mm. Hg) with a normal pulmonary wedge pressure (3 mm. Hg). Cardiac output was normal. Resting arterial oxygen saturation was 90 per cent. During periodic breathing his arterial oxygen saturation fell to 75 per cent.

The patient remained hospitalized for 6 weeks, during which period he was given an 800-calorie low-sodium diet. His weight declined to 243 pounds, with a steady improvement in dyspnea and somnolence. He was discharged on the same diet and digitoxin, 0.15 mg. daily.

The patient returned 6 months later for further study. He had lost weight to 233 pounds and still complained of mild dyspnea on exertion. There were no other signs or symptoms of congestive heart failure, but digitoxin was continued.

*Case 4 (N. S.)**

A 41-year-old white man was admitted to Duke Hospital in November 1954 for evaluation of lifelong obesity. Between the age of 16 and 26 years the patient weighed from 240 to 250 pounds. On occasions, with dieting, his weight decreased to 200 pounds. One year before admission he weighed 380 pounds. He continued to gain weight rapidly to the time of admission. With the rapid weight gain the patient had noted marked somnolence and would fall asleep when seated. Exertional dyspnea, orthopnea, and ankle edema had been present for 6 months.

On admission the patient was markedly obese, somnolent, dyspneic, and cyanotic with Cheyne-Stokes respiration. His weight was 462 pounds, his height 69 inches. Blood pressure was 170/110 mm. Hg, pulse rate 110 and respiratory rate 20 per minute. The remainder of the physical examination was remarkable only in the marked obesity and the presence of brawny edema of the lower abdomen and legs.

The hemoglobin level was not determined but the hematocrit value was 60 volumes per cent. The white blood count was 9,500, with a normal differential count. Urinalysis revealed a specific gravity of 1.018, no sugar, and a trace of protein. The fasting blood sugar was 111 mg., the blood cholesterol was 154 mg. per 100 ml., carbon dioxide combining power was 42.3 mEq. per L. Chest x-ray showed cardiac enlargement and increased lung markings. Skull films were negative. Right axis deviation was present on the electrocardiogram. Urine gonadotropin and 17-ketosteroid excretions were within normal limits.

The patient was placed on a reduction diet and 2 months later his weight was 342 pounds, representing a loss of 120 pounds. Digitalis and mercurial diuretics were not used, though salt intake was restricted as part of the reduction diet. He was less somnolent and less dyspneic on exertion. He had no orthopnea, and Cheyne-Stokes breathing occurred only intermittently with deep sleep. The hemoglobin was 16 Gm. per 100 ml.

The diet was followed closely and 1 year later the patient weighed 286 pounds and no longer had exertional dyspnea, ankle edema, somnolence, or Cheyne-Stokes breathing. At this time the hemoglobin was 15.7 Gm. per 100 ml.

Case 5 (R. G.)

A 44-year-old white farmer was admitted to Duke Hospital in May 1955 because of substernal pain that had been present for 1 day. The patient first began to gain weight about 15 years before admission and reached a maximum of 268 pounds 2 to 3 years before admission. At that time he noted exertional dyspnea, orthopnea, occasional episodes of paroxysmal nocturnal dyspnea, and ankle edema. The patient had somnolence during this period and his family commented on his irregular breathing during sleep. The somnolence and irregular breathing were so severe that the patient's family and friends often urged that he seek medical aid. The past history was otherwise negative except for bouts of epigastric pain occurring before meals and relieved by food and antacids.

On physical examination the patient was obese and somnolent, weighed 230 pounds, and was 70 inches in height. The blood pressure was 140/100 mm. Hg, the pulse rate was 80 per minute, the respiratory rate was 12 per minute with Cheyne-Stokes breathing during sleep (fig. 2). The optic fundi were normal. There were scattered rhonchi throughout the chest. Cardiomegaly and abdominal obesity were present, but there was no peripheral edema.

Pertinent admission laboratory data included a hemoglobin of 20 Gm., a hematocrit of 61 volumes per cent, and a white blood count of 8,950. Urinalysis showed a specific gravity of 1.013 and a 1 plus protein. Fasting blood sugar initially was 145 mg. per 100 ml.; when repeated later it was found to be 110 mg. fasting and 145 mg. per 100 ml. 2 hours after a meal. The blood cholesterol was 401 mg. per 100 ml. The electrocardiogram showed slight right axis deviation. Chest x-ray revealed cardiomegaly, and skull films were negative. A gallbladder series

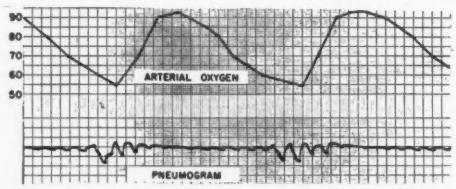

FIG. 2. Variation in arterial oxygen saturation (*ordinate*, per cent) with various phases of Cheyne-Stokes breathing, case 5 (R. G.). Arterial oxygen values were read from an ear oximeter.

* Courtesy of Dr. Walter Kempner.

was negative, and gastrointestinal series showed only indirect evidence of a duodenal ulcer. Urinary 17-ketosteroid and gonadotropin excretions were within normal limits. The patient had no recurrence of chest pain, and serial electrocardiograms revealed no evidence of myocardial infarct. After 2 weeks on an 800-calorie reduction diet, he was discharged. He had lost only 5 to 6 pounds, and had improved only in that he was less somnolent. When seen 2 weeks later, he had failed to lose weight, and has since failed to return for follow-up.

Case 6 (S. W.)

A 28-year-old unemployed Negro man was admitted to Duke Hospital in April 1954 for investigation of marked obesity. At age 10 years, the patient weighed 125 pounds and continued to gain in association with excessive intake of food. The patient weighed 355 pounds at age 20 and 550 pounds at the time of admission. The estimated food intake during this period was 11,000 calories per day. Somnolence had been noted for several years, more marked in the year before admission. During the previous year the patient had also noted ankle edema, orthopnea, and exertional dyspnea. Cheyne-Stokes breathing during sleep was described by the family. Polyuria, polydipsia, and nocturia had also been observed for a period of 6 to 8 months before admission.

On physical examination the patient weighed 555 pounds and was 74½ inches tall (fig. 3). The blood pressure was 210/160 mm. Hg., pulse rate was 140 per minute, and the respiratory rate was 23 per minute. Prominent physical findings were striae over the shoulders and buttocks, massive obesity, and 4-plus pretibial edema. Neurologic examination was negative. Rectal examination revealed thrombosed and bleeding hemorrhoids.

The accessory laboratory findings included a hemoglobin of 12.1 Gm., a white blood count of 7,900, a urine specific gravity of 1.022, with 1 plus proteinuria and 1 plus sugar. Repeat urine analysis did not show glycosuria. The fasting blood glucose was 111 mg. and 113 mg. per 100 ml. 2 hours after eating. The carbon dioxide combining power was 35.7 mEq. per L., and the cholesterol was 135 mg. per 100 ml. Urinary excretion of gonadotropins and 17-ketosteroids was slightly low. Skull films were negative. Chest x-ray was impossible because of the marked obesity. Electrocardiogram showed no axis deviation. T waves were inverted in leads I and aV_L and flat in V_5 and V_6; they were thought to be compatible with left ventricular ischemia.

After these studies it was believed that the patient's excessive obesity was solely the result of his tremendous food intake, and he was discharged on a reduction diet.

The patient did not follow his diet and was readmitted to the hospital in June 1955. He had gained weight to 598 pounds and was more dyspneic.

FIG. 3. Photograph, case 6.

Physical examination was essentially unchanged except that the patient was obviously more obese.

The admission hemoglobin was 12.0 Gm. per 100 ml., and urinalysis showed 1- to 2-plus proteinuria and no sugar. The fasting blood sugar was 108 mg., and the blood cholesterol 85 mg. per 100 ml. Other laboratory values were a blood carbon dioxide combining power of 32 mEq., a serum sodium of 148 mEq., and a serum potassium of 4.5 mEq. per L. Radioactive iodine uptake was 18 per cent. Skull x-rays were again negative and chest x-ray was not possible. The electrocardiogram showed no axis deviation, atrial flutter, and nonspecific T-wave changes. An initial stool specimen was guaiac positive, which was thought to be related to bleeding hemorrhoids. A later stool revealed no occult blood.

The patient was placed on an 800-calorie low-sodium diet and after 1 week was digitalized with

1.2 mg. of digitoxin and maintained on 0.1 mg. of digitoxin daily. In 2 weeks the patient had lost 44 pounds and showed moderate symptomatic improvement, but continued to be somnolent with marked periodic breathing during sleep. At this time the patient was given 10 mg. of dextroamphetamine (Dexedrine) daily to decrease his somnolence, and started on active program of exercise by the physiotherapy department. Four weeks later he had lost 94 pounds, was no longer drowsy or orthopneic, and had less exertional dyspnea. Ten weeks after the above program was instituted the patient had lost 143 pounds, weighing 455 pounds. After discharge the patient did not follow the diet, and the progressive decline in weight observed in the hospital did not continue. He remained markedly improved, however, and found employment as a ditch digger and plasterer. During this time he complained of moderate ankle edema, but no exertional dyspnea, orthopnea, or somnolence.

Review of Literature

The authors are not the first to recognize such a syndrome associated with extreme obesity. Grant has studied several such cases,[1] one of which came to postmortem examination and was found to have marked right ventricular hypertrophy and advanced pulmonary siderosis, with no hemosiderin in other areas. He postulated that this was related to a combination of unusual oxygen requirements and a mechanical ventilatory impairment, both secondary to obesity. The existence of such a syndrome was first suggested to the authors by Dr. Robert P. Grant, who reviewed the electrocardiograms of case no. 1.

Previous published reports have described one or more features of the syndrome in extremely obese patients. Spitz[2] reported 3 obese patients with narcolepsy, periodic breathing, and somnolence. At autopsy, 2 of these patients had findings compatible with Cushing's syndrome. The third improved with weight reduction, with disappearance of the polycythemia and narcolepsy. One of the 2 autopsied cases had hypertrophy of both ventricles with marked left ventricular dilatation. During life this patient had had left axis deviation on the electrocardiogram. The other autopsied case had marked hypertrophy of the right ventricle. During life this patient had a normal electrocardiogram. The third patient, who improved on weight reduction, had hypertrophy and dilatation of the left ventricle on chest film, but marked right axis deviation by electrocardiogram. Though all of Spitz's cases show certain features of the syndrome, the third case seems to fit all the criteria, including improvement with weight reduction.

Olsen and Wilius[3] reported a male patient with extreme obesity, congestive failure, marked dyspnea, cyanosis, and polycythemia. The electrocardiogram revealed marked right axis deviation. With weight reduction from 302 to 277 pounds, diuresis, and 3 venesections, he was greatly improved symptomatically. The illness was thought to be related to pulmonary arteriolar sclerosis (Ayerza's disease) and hypertensive vascular disease, though the blood pressure ranged from 94/74 to 145/92 during the period of observation.

Cutting[4] has emphasized the frequent coexistence of obesity and narcolepsy suggesting that both might be of hypothalamic origin. Polycythemia is also pointed out as a frequent finding in narcolepsy. Three cases were cited.

Auchincloss, Cook, and Renzetti[5, 6] have reported a markedly obese patient with cyanosis, polycythemia, and heart failure in whom detailed pulmonary function studies and cardiac catheterization were carried out. The markedly reduced arterial oxygen saturation (30 per cent) and the carbon dioxide retention seen in this patient were thought to be caused by alveolar hypoventilation. The pulmonary arterial pressure was elevated (95/50).

Weil and Prasad[7, 8] have reported 5 markedly obese patients with marked polycythemia, in 3 of whom the polycythemia was reversed by weight reduction alone. These patients were found to have a decreased vital capacity, a decreased arterial oxygen saturation, and an elevated serum carbon dioxide content. Polycythemia was thought to be a result of hypoxia resulting from poor ventilation.

Johnson, Lillehei, and Miller[9] have studied 2 patients with extreme obesity, arterial oxygen unsaturation, and carbon dioxide retention. These patients demonstrated profound alterations in pulmonary ventilation and blood flow, particularly in the supine position. In this position there was a rise in intrathoracic pressure and a decrease in total lung volume and func-

tional residual capacity. The effective diffusing capacity of the lung was decreased, and the work of breathing greatly increased in the supine position. Other studies suggested the appearance of a true right-to-left shunt in the supine position. All these alterations were thought to be entirely related to obesity.

Benaim and Worster-Drought[10] have reported an individual with dystrophia myotonica of the diaphragm, with pulmonary hypoventilation and secondary polycythemia. This individual was also obese. Other cases fitting the syndrome have been reported by Burwell[11] and Counihan.[12]

Discussion

The similarity of the 6 patients reported here and those cited suggests that the occurrence of somnolence, cyanosis, polycythemia, and congestive heart failure in conjunction with severe obesity is not a mere chance relationship but a true syndrome (fig. 4). The degree of obesity necessary for the development of the syndrome is not well defined. Several patients were obviously obese but at least 2 of the group were only obese when considered in relation to their height. Case 5, though complicated by possible arteriosclerotic heart disease, illustrates this point. In these individuals the excess weight was mainly confined to a large protuberant abdomen. It should be noted that most of the patients had gained large amounts of weight in the 6 to 12 months prior to onset of symptoms.

All were somnolent, and during sleep had a type of Cheyne-Stokes breathing. This type of breathing differed from the usual Cheyne-Stokes breathing seen in heart failure in that the periods of apnea and hyperpnea were shorter than usual, being 10 to 20 seconds in duration. All had evidence of hypoventilation during sleep, and in those patients in whom measurements were made, there was arterial oxygen unsaturation and elevation of carbon dioxide tension. In cases 2 through 6, the degree of arterial oxygen unsaturation was remarkably variable, usually in relation to the cycles of Cheyne-Stokes breathing. In case 1 the level of arterial oxygen saturation was not measured. In all in whom the observation was made, the cyanosis could be quickly reversed by several deep breaths or by inhalation of 100 per cent oxygen. Detailed data from cardiac and pulmonary function studies on these and other obese patients will be presented elsewhere.[13]

	N.S.	E.F.	J.D.	R.P.	R.G.	S.W.
MARKED OBESITY	+	+	+	+	+	+
SOMNOLENCE	+	+	+	+	+	+
PERIODIC BREATHING	+	+	+	+	+	+
INTERMITTENT CYANOSIS	+	+	+	+	+	+
POLYCYTHEMIA	+	+		+	+	
EKG - RIGHT AXIS	+	+	+		+	
HEART FAILURE		+	+	+		
SYNDROME REVERSED BY WEIGHT REDUCTION	+	+	+	+		+

Fig. 4. Summary of findings in the 6 cases reported.

Polycythemia occurred frequently, but was not always pronounced. One patient (S. W.) was anemic, which may have been the result of hemorrhoidal bleeding. A rightward electric axis was common but not always observed. On the other hand, none of the patients had left axis deviation or horizontal electric axis as would be expected in an obese patient. Not all of the patients had clinical evidence of congestive heart failure. The presence or absence of failure may be related to the stage of the illness and the presence of other unknown factors. Furthermore, the clinical impression of congestive heart failure was difficult to evaluate because dyspnea, orthopnea, and ankle edema could be related to the obesity.

Additional laboratory studies indicated that the syndrome observed was not related to a recognizable endocrinopathy such as Cushing's syndrome. It is of interest that the patients had a high oxygen consumption and a low blood cholesterol.

The correction of the findings with weight reduction in 5 of the 6 patients suggests that obesity is the primary etiologic factor. The dietary restriction used in these patients caused a rapid decrease in weight except for case 5, who failed to lose significant weight during the period of observation. In 5 of the 6 patients, digitalization was carried out and mercurial diuretics were used at the same time that weight reduction was begun. In case 4, the symptoms were reversed by weight reduction

alone, and in case 1 and 2, the symptoms have failed to recur after omission of digitalis and diuretics. For this reason weight reduction is considered to be the most important factor in treatment. The reversibility of the signs and symptoms of heart failure with weight loss is believed to be of significance in that it adds another to the list of reversible disorders causing congestive heart failure.

The signs and symptoms of congestive failure, when present, responded quickly to digitalis, diuretics, and salt restriction. Somnolence, Cheyne-Stokes respirations, and intermittent hypoxia persisted, however, disappearing only as weight loss progressed. In an attempt to reverse these latter findings more quickly, amphetamine was used in conjunction with diet in case 6, and was found to be effective in markedly reducing the degree of somnolence, the occurrence of Cheyne-Stokes breathing, and the hypoxia.

The exact relationship between obesity and the various features of the syndrome remains largely speculative. The somnolence and the Cheyne-Stokes respirations are presumed to be of central origin, yet the mechanism of their production remains unknown. They have been observed to disappear with weight reduction; therefore they are assumed to be related to the obesity. The question may be raised of the role of cerebral anoxia or hypercapnia in their production, yet other patients, i.e., those with congenital heart disease and chronic lung disease, have similar changes in blood gases without such symptoms.

The somnolence and Cheyne-Stokes respirations result in periodic hypoventilation, which is especially marked in sleep. Associated with these periods of hypoventilation there are remarkable drops in arterial oxygen saturation. The mechanism of the rapid fall in arterial oxygen saturation seems reasonably well established from studies of pulmonary function in these and other obese subjects.[13] They have been found to have a striking reduction in expiratory reserve, especially with recumbency. Thus there is a smaller "reserve" of oxygen at the end of a normal expiration. At the same time the total consumption of oxygen in such obese subjects is very large. These features combine to produce a rapid fall in arterial oxygen saturation with breath holding or with the apneic phase of Cheyne-Stokes respiration.

The polycythemia seen in 4 of the 6 patients in this group is thought to be related to prolonged arterial oxygen unsaturation. The chief feature distinguishing it from polycythemia vera is its reversibility with weight reduction.

The mechanism of the heart failure and indeed its nature are obscure. Borderline hypertension has been seen in several subjects, but is thought to be due largely to the error of indirect blood pressure measurement in the obese individual. The roentgenograms of the chest were most often described as showing left ventricular enlargement or generalized cardiac enlargement. The electrocardiograms, though showing right axis deviation on standard and unipolar limb leads, show a posterior orientation of the QRS vector in space, rather than the anterior orientation usually seen in right ventricular hypertrophy. The electrocardiographic findings and the manner of their reversal are suggestive of the verticalization of the electric field seen with pulmonary emphysema, which is perhaps a distortion of the electric field as a result of the presence of poorly conducting, overdistended lungs. Obesity could conceivably produce similar changes as a result of the presence of epicardial fat, yet it is difficult to see why the change to a right axis is not seen more commonly in obese subjects if this is the case. At the present time, the electrocardiographic changes are considered to be secondary to changes in the heart, not to a recording artifact secondary to obesity. It seems more likely that the changes are a result of increased pressure on the right side of the heart or an increased relative size of the right side of the heart.

Cardiac catheterization is carried out with great difficulty in such patients because of their huge size and the resultant difficulty in visualization of the catheter during the procedure. In those that have been done, pulmonary arterial pressures have been moderately elevated. These patients show considerable variability of pulmonary arterial pressure during a single study. This has not been correlated with changes in arterial oxygen saturation, but is perhaps related to periodic anoxia. The authors

have had no opportunities for postmortem study of such cases. As previously stated, in the only known case in which the heart has been examined post mortem, right ventricular hypertrophy was present.

On the basis of present information it is postulated that the hypoventilation associated with periodic breathing especially during sleep, leads to hypercapnia and hypoxia, and that these in turn contribute to the development of polycythemia, pulmonary hypertension, right-sided cardiac enlargement, and ultimately to heart failure. Additional studies are needed to prove many of the steps in the above postulation.

Summary

A syndrome consisting of somnolence, cyanosis, periodic breathing, polycythemia, right axis deviation, and the clinical picture of congestive heart failure has been seen in a group of markedly obese patients. The symptoms and findings appear to be related to obesity and were, in most instances, reversed by weight reduction. It is postulated that hypoventilation leads to hypercapnia and hypoxia, and that these contribute to the development of polycythemia, pulmonary hypertension, right-sided cardiac enlargement, and ultimately to heart failure.

Summario in Interlingua

Un syndrome consistente de somnolentia, cyanosis, respiration periodic, polycythemia, e le tableau clinic de congestive disfallimento cardiac esseva notate in un gruppo de marcatemente obese patientes. Le symptomas e le constatationes clinic esseva apparentemente connectite con le obesitate. In le majoritate del casos illos esseva revertite per reduction de peso. Es postulate que hypoventilation produce hypercapnia e hypoxia e que istos contribue al disveloppamento de polycythemia, hypertension pulmonar, allargamento dextero-cardiac, e ultimemente disfallimento cardiac.

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Science is a permanent record of premises, deductions, and conclusions, verified all along the line by its correspondence with facts.—A. N. Whitehead. *Aims of Education*, 1929.

Association of Aortic Valvular Disease and Cystic Medial Necrosis of the Ascending Aorta

Report of Four Instances

By VICTOR A. MCKUSICK, M.D., R. BRUCE LOGUE, M.D., AND HENRY T. BAHNSON, M.D.

In 4 patients with aortic stenosis and regurgitation, progressive dilatation of the ascending aorta and dissecting aneurysm developed. Cystic medial necrosis was discovered histologically. It is suggested that the change in the aorta is secondary to hemodynamic stresses imposed by the disease at the aortic valve.

IN 4 patients we have observed the association of aortic stenosis with large fusiform and dissecting aneurysm in the ascending aorta. In each case Erdheim's cystic medial necrosis was present. It is our purpose, in describing these cases, to suggest that the association is more than coincidence.

CASE REPORTS

Patient 1. A. H. (J. H. H. 714094), a 31-year-old male school teacher, was first told he had a heart murmur when he was 15 years old. There was no history suggestive of rheumatic fever. The patient was completely asymptomatic and engaged actively in athletics. He remained well until the spring of 1953, when he had an attack of severe substernal pain lasting 10 to 12 hours. A roentgenogram of the chest was interpreted as normal. (On later review dilatation of the ascending aorta was suspected.) Thereafter he noted that his physical stamina was somewhat reduced. He could, however, walk a mile or more and climb stairs without dyspnea. Beginning May 15, 1955, he again developed substernal pain in mild attacks lasting 30 to 40 minutes, not clearly related to exertion and occurring mainly on first arising in the morning. Furthermore, increasing dyspnea and fatigue with exertion were noted.

The patient's habitus was in no way unusual. He was heavy-set, athletically built, and well muscled. The pulse was small in volume and the pulse pressure somewhat narrow (blood pressure, 114/84 mm. Hg). There was an active systolic pulsation in the second right intercostal space. On auscultation the predominant finding was a loud systolic murmur in the right second interspace, transmitted up the right side of the neck. It was also audible to some extent at the apex. The second aortic sound was quite distinct and there was a faint, early, decrescendo diastolic murmur. At the base of the neck in the region of the lower end of the sternocleidomastoid muscle, there was a peculiar, high-pitched systolic "coo."

Fluoroscopy revealed marked enlargement of the ascending aorta to the right. An electrocardiogram showed left axis deviation and a pronounced pattern of left ventricular strain.

Thoracotomy was performed on August 31, 1955, through a right anterolateral incision. The ascending aorta was found to be dilated to about 30 cm. in circumference. It diminished in size at the end of the ascending portion to measure 15 cm. just proximal to the innominate ostium, beyond which point the aorta seemed to be of normal caliber. There was a mass of fibrin and fibrous tissue suggesting previous inflammation on the anterior surface of the ascending aorta. The ascending aorta was mobilized and almost half its circumference was excised. In this process it became apparent that there was a dissection in the wall of the ascending aorta. A finger was introduced into the aorta through a diverticulum sutured to the aorta, and the aortic valve was palpated. The right anterior commissure was fused and the 2 cusps adjacent to it constituted almost a single large cusp. Calcified, rigid areas were felt. The other 2 commissures were free; the tip of the finger could be fitted through the orifice and, in general, the stenosis was not thought to be of high grade. Finger-fracture of the aortic valve was not attempted for fear of aggravating the hemodynamic disturbance at that site. The ascending portion of the aorta was wrapped in a Nylon sculteus binder.* At the close of the procedure the ascending portion of the aorta was uniformly 12 to 13 cm. in circumference.

Histologic study of the removed aortic tissue showed cystic medial necrosis.

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* Surgical features of this and the following case have been described elsewhere[1] and illustrated by means of chest x-rays and artist's sketches of the findings at operation.

Postoperatively the patient has done well. That he has no longer had chest pain suggests that the preoperative pain may have been caused by the aneurysm and did not represent myocardial ischemia. Exercise tolerance is probably increased and certainly no less than before operation. The "coo" at the base of the neck on the right persists in apparently unaltered form.

Patient 2. T. G. M. (726673), a 50-year-old attorney, had numerous episodes of acute tonsillitis during his youth in a southern state but recalled no frank rheumatic fever.

At the age of 24 years he was first told that he had mitral stenosis. At the age of 35 years he was twice rejected for service in the Merchant Marines and in the Army because of murmurs. He was still asymptomatic. Exertional dyspnea had its onset at the age of 43 years and soon thereafter attacks of paroxysmal nocturnal dyspnea developed. Aortic aneurysm was discovered when he was 48 years old. Chest pain was never a conspicuous feature.

Physical examination revealed a blood pressure of 198/94 mm. Hg in both arms, 235/108 in both legs. There was an active, expansile, systolic pulsation in a large area below the right clavicle and the same area was dull to percussion. In this same area, furthermore, there was a grade IV systolic murmur accompanied by a thrill and followed by a decrescendo diastolic murmur typical of aortic regurgitation. What seemed to be the same diastolic murmur was heard out toward the right axilla, where it acquired a delicate high-pitched quality, down the left sternal border, and in the apical area, where its quality was more low pitched and rumbling. The heart was strikingly enlarged to the left. Atrial fibrillation was present.

In general nothing about the patient's habitus or family history suggested the Marfan syndrome. The ophthalmologist could find no evidence of ectopia lentis.

Roentgenograms showed a large aneurysm of the ascending aorta and considerable enlargement of the left ventricle.

An operation similar to that used in the first patient was planned and at thoracotomy an enormous aortic aneurysm was discovered as anticipated. After application of clamps and excision of the occluded portion of the aorta, it was found that dissection had in fact occurred with a characteristic sheathlike double channel in the ascending aorta. The false channel was traversed by typical fibrous cords. The surgical procedure was performed according to plan without evidence of cardiac embarrassment. Soon after the clamp was removed from the aorta, pulsations of the heart became weak and ventricular fibrillation began. Cardiac massage and other efforts at resuscitation were of no avail.

At autopsy the heart weighed 900 Gm., the excess weight being mainly the result of left ventricular hypertrophy. There was calcific aortic stenosis

FIG. 1. Autopsy specimen (patient 2) showing stenosis of tricuspid aortic valve and adjacent dissection of the ascending aorta.

with fusion of 1 commissure, and the valve also appeared regurgitant (figs. 1 and 2). An aortic dissection extended from 4 cm. above the aortic valve through the end of the aortic arch and into the innominate and subclavian arteries. The thoracic aorta was of normal size. Microscopic study showed cystic medial necrosis in the ascending aorta and to much less extent in the subclavian, mesenteric, and pulmonary arteries and abdominal aorta.

*Patient 3.** W. M., a 40-year-old man, had known for many years that he had valvular heart disease, presumably rheumatic. Previously a diagnosis of aortic stenosis and regurgitation had been made. He had never experienced symptoms referable to the cardiovascular system and his exercise tolerance

* Case 8 in a series of dissecting aneurysm previously reported by one of us.[2]

FIG. 2. Close view of stenotic aortic valve in figure 1

had always been normal. On the day of admission to the hospital he developed a slight pain at the base of the neck that was followed shortly by a severe precordial pain.

Examination showed a man of normal habitus with no evidence of the Marfan syndrome. The blood pressure was 110/90 mm. Hg in the right arm and 120/100 in the left arm. The blood pressure was not recorded in the legs. The heart was enlarged to the left. There was a pronounced systolic propulsion at the second and third right intercostal spaces. A harsh systolic murmur, with accompanying thrill, was heard over the precordium with maximal intensity at the first and second right intercostal spaces adjacent to the sternum. The murmur was transmitted to the carotid arteries. The aortic second sound was diminished. The lungs were clear. The remainder of the examination revealed no significant abnormalities.

Following the administration of an opiate the pain gradually subsided. Six days after admission the patient suddenly died.

Autopsy revealed the weight of the heart to be 650 Gm. There was advanced calcific aortic stenosis with thickening of the mitral chordae tendineae. Death was caused by hemopericardium due to rupture of a dissecting aneurysm. There was an intimal tear 2.5 cm. above the aorta and the dissection extended through the length of the aorta and in a retrograde fashion to rupture into the pericardial sac. Cystic medial necrosis was noted in the microscopic sections of the aorta; there was no evidence of rheumatic lesions in the aorta.

Patient 4. M. I., a white male student of theology, age 27, had been known to have a heart murmur since the age of 3. There was no history of rheumatic fever, and he had never had symptoms referable to the cardiovascular system. In 1948, an x-ray of his chest showed dilatation of the ascending aorta with a heart of normal size (fig. 3*A*). On the day of admission he suddenly developed severe constant dull aching substernal pain extending from the epigastrium to the neck. The pain increased in severity, and he was admitted to the student infirmary.

Physical examination showed no evidence of the Marfan syndrome. The blood pressure was 106/84 mm. Hg in both arms; it was not recorded in the legs. The heart was normal in size. The cardiac rhythm was regular. There was a harsh, grade III systolic murmur accompanied by a systolic thrill at the first and second right intercostal spaces.

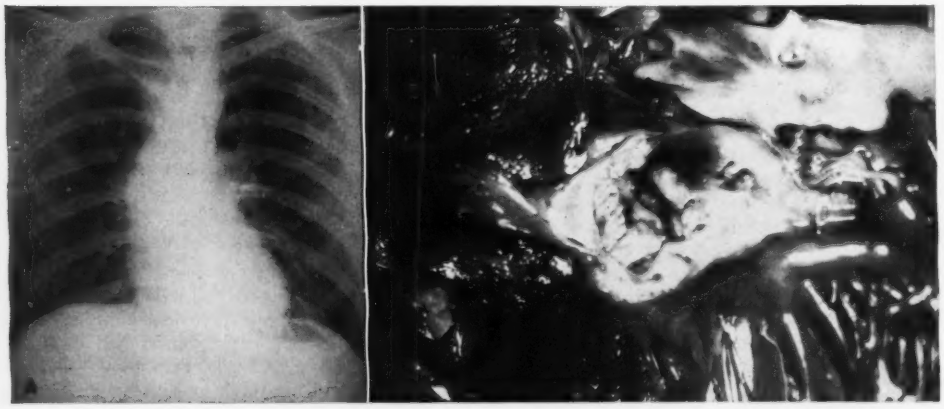

FIG. 3. *A*. X-ray of chest taken 1 year before death in patient 4. Note the "poststenotic dilatation" of the aorta. *B*. Necropsy specimen in patient 4 with aortic valve viewed from the left ventricle.

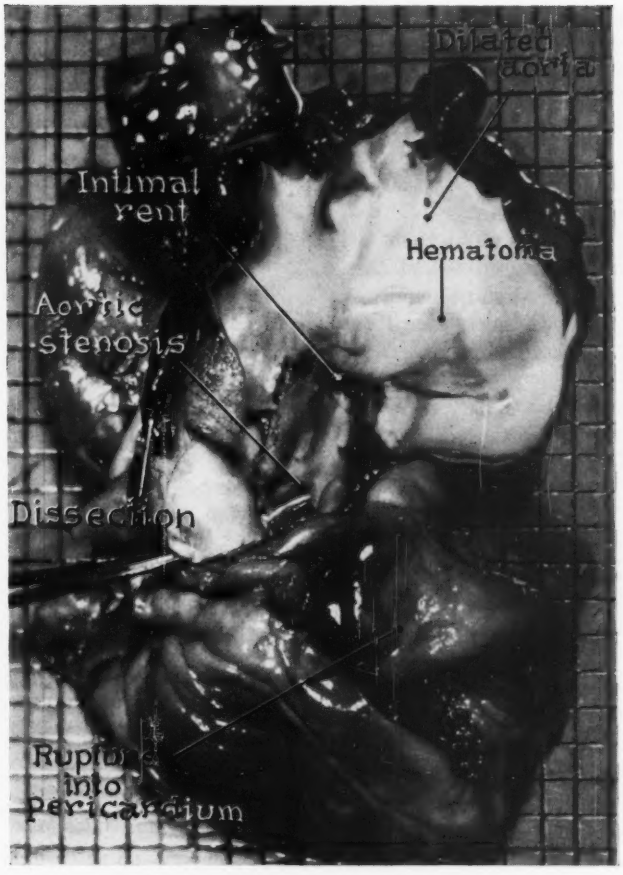

FIG. 4. Necropsy specimen of heart and aorta of patient 4.

The aortic second sound was replaced by a faint, early, high-pitched, blowing diastolic murmur. The systolic murmur was transmitted over the precordium toward the apex. The first sound at the apex was normal. The systolic murmur was not transmitted to the axilla. No diastolic murmurs could be heard at the apex. The lungs were clear and resonant. Liver and spleen were not tender or palpable. The remainder of the examination was normal. An electrocardiogram taken the day after admission showed left ventricular hypertrophy. On the following day the electrocardiogram showed changes consistent with acute pericarditis. During his hospital stay the patient continued to complain of chest pain requiring opiates for relief. During the following 3 days the pain became less severe; 4 days after admission, however, there was an increase in severity of chest pain associated with sudden gasping respirations that continued for 10 minutes, when he died.

Autopsy showed aortic stenosis (fig. 3*B*) with some calcification of the valve and with left ventricular hypertrophy. There was no evidence of rheumatic involvement of the mitral valve and the aortic stenosis was thought to be of congenital origin. There was a dissecting aneurysm, which began within the first few centimeters of the aortic valve in the area of dilated aorta. There was retrograde extension of the dissection with rupture into the pericardial sac. Death occurred as a result of tamponade (fig. 4). Microscopic examination showed cystic medial necrosis of the aorta.

DISCUSSION

As is so often the case, whether the aortic valve disease was of rheumatic, congenital, or other origin in these instances cannot be stated with certainty. In the fourth patient, the history of murmur from the age of 3 years and the

absence of rheumatic stigmata by history or necropsy satisfy the usual criteria for congenital aortic stenosis.[3] In the second patient the minor changes in the mitral chordae tendineae at necropsy and the history of frequent tonsillitis in youth are consistent with a rheumatic etiology. Changes in the mitral chordae tendineae were present also in the third patient.

In all 4 patients the stenosis of the aortic valve was only moderately severe and aortic regurgitation was also present in some degree. These may be important considerations in connection with development of changes in the ascending aorta.

If instances of cystic medial necrosis in association with coarctation of the aorta are excluded, of 4 patients seen at the Johns Hopkins Hospital in the last 2 years with large aneurysm of the ascending aorta associated with cystic medial necrosis, 2 had aortic valvular disease and are reported above as patients 1 and 2. The etiology in the other 2 patients is completely obscure. Mattison and Cluff[4] have put on record 1 of these other cases.

In the second patient, there was no history one could relate to acute dissection of the ascending aorta although such a history was present in the first patient and was the presenting and predominating feature of patients 3 and 4.

The finding in the second patient of widespread cystic medial changes in the mesenteric, pulmonary, and subclavian arteries as well as throughout the aorta is disturbing to the theory that the changes in the ascending area are the result *solely* of hemodynamic stresses related to the disease of the aortic valve.

The presence of an unusual musical systolic "coo" over the innominate-carotid-subclavian axis in case 1 is of note. This was seemingly completely distinct from the murmur of aortic stenosis, which was of conventional quality. In other cases of dissection in the ascending aorta, musical murmurs, in either systole or diastole,[5] have been heard over the course of the aorta. Anatomically at least 2 types of anomalous structures are present and might be playing a role: (1) fiddle-string bands usually traverse the false channel in the ascending aorta; (2) lips are created at the site of the initiating intimal tear or distally at the site of re-entry. Partial occlusion of a vessel at the arch of the aorta may be the mechanism in the patient described here; although the murmurs resulting from occlusive arterial disease are generally noisy, occasionally they may be musical. A musical murmur well localized to the base of the neck or just below the clavicle on the right, especially if it develops abruptly or is changeable, is a sign suggesting dissecting aneurysm.

Other Cases. Reviewing cases of dissecting aneurysm in persons 40 years of age and less, Schnitker and Bayer in 1944[6] found that of 141 such cases reported in the literature, rheumatic valvular disease had been present in 9. Aortic stenosis was present in 1, and in a second there were combined lesions of the aortic and mitral valves. The remaining 7 cases were reported to have had mitral lesions.

Under the title of "Congenital Aortic Aneurysm with Valvular Stenosis and Dissecting Aneurysm," Petch,[7] in 1952, described a 35-year-old man in whom a cardiac murmur had been heard from the age of 5 years and noted again during a period of service in the army. There was no history of rheumatic fever. Fatal dissection with rupture into the pericardial sac occurred. Autopsy revealed fusion of the 2 posterior aortic cusps and calcification of the valve.

Lewes[8] found 1 instance of dissecting aneurysm among 25 cases of aortic stenosis. The patient (case 7), a 65-year-old man, had a small pulse but a blood pressure of 105/75 mm. Hg. There was no evidence of associated aortic regurgitation. Anatomically the grade of stenosis was considered to be moderately severe. Cystic medial necrosis was present in the aorta.

No other cases precisely like those presented here have been found, although a comparable situation does occur in coarctation of the aorta in which dissection beyond the stenosis may occur.[9-13]

Since it was first noted by Chevers[14] of Guy's Hospital in 1842,* poststenotic dilatation of the

* In a communication entitled "Observations on the Diseases of the Orifice and Valves of the Aorta," Chevers wrote as follows:

> The valves themselves may either have become adherent at portions of their edges, or have suffered extreme thickening from the conversion

ascending aorta (fig. 3*A*) has been frequently observed with aortic stenosis of either rheumatic or congenital origin.[3, 15] At times the dilatation has attained relatively mammoth proportions, especially in cases of aortic stenosis of only moderate severity.[8, 16-18]

Cystic Medial Necrosis. The 2 clearest clinical associations with cystic medial necrosis of the aorta are hypertension and genetic inferiority of the aortic media, of which the Marfan syndrome[19] is the most familiar example. In patients in whom congenital aortic stenosis is suspected, a congenital weakness of the aorta cannot be excluded but is unlikely in our opinion. In general, cystic medial necrosis may be a nonspecific morphologic expression of structural fatigue in a normal aorta subjected to unusual hemodynamic stresses or in a genetically inferior aorta exposed only to the usual stress. Aging, in the sense of accumulated physiologic stresses, seems to be another factor. Whatever the precise mechanics, disease of the aortic valve appears to result in a poststenotic hemodynamic set-up that is unusually stressful to the aorta. The occurrence of cystic medial necrosis in association with aortic stenosis seems to be more than coincidence.

of nearly the whole of their curtains into rigid masses of calcareous substance—conditions which are productive of impediment to the passage of the blood from the ventricle. In cases of this description, I have observed that the aorta, at a short distance above its valves, becomes considerably dilated, its walls at the same time appearing remarkably thin. It might, at the first glance, be expected that, in this disease, as the blood really has great difficulty in entering the artery, a contrary state of the vessel would occur, and that the whole of its canal would become diminished in calibre; but the dilatation probably results from the long continuance of a degree of stagnation in the contents of the tube, the thickened and narrowed state of the passage preventing the systolic impulse of the ventricle from being conveyed into the vessel with sufficient force to propel the blood freely through the arteries. It may also be in great measure due to the fixed and hardened state of the valves, which instead of yielding with a moderate degree of elasticity under the pressure of the blood during the ventricular diastole, remain perfectly rigid, and, in this way, cause the whole of the blood contained in the artery to fall upon the sides of that vessel, which are thus compelled to yield. The thinning of the vessel's tunics evidently arises from the loss of their elastic power, in consequence of the long-continued over distension.

Summary

A clinical syndrome—the association of disease of the aortic valve (stenosis and regurgitation) with diffuse aneurysm of the ascending aorta with or without dissection—is described on the basis of 4 patients in whom dissection occurred. Histologically, cystic medial necrosis of the aorta was present. It is suggested that this association represents further evidence that cystic medial necrosis of the aorta is a nonspecific result of hemodynamic stress on the aorta.

Summario in Interlingua

Un syndrome clinic—le association de morbo del valvula aortic (stenose e regurgitation) con aneurysma diffuse del aorta ascendente con o sin dissection—es describite super le base del casos de 4 patientes in qui dissection occurreva. Ab le puncto de vista histologic, cystic necrose medial del aorta esseva presente. Es formulate le opinion que iste association representa un prova additional que cystic necrose medial del aorta es un resultato non-specific de stress hemodynamic in le aorta.

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A CARDIOLOGIST'S HIPPOCRATIC OATH

Perhaps the physician should have a personal creed in respect to the handling of patients, and particularly apprehensive ones. Such a creed might consist of something like the following.

First, I shall avoid any thoughtless expression, deed or statement that might initiate, in a healthy or relatively healthy patient, the idea that the heart is abnormal; briefly, I shall not be a party to iatrogenic heart disease.

Second, I shall not bring precise instrumental and laboratory methods, such as electrocardiography, into disrepute by consciously gainful or ignorant misinterpretation.

Third, I shall discourage excessive dependence of any patient on a physician, but I shall give freely of time and try to think of satisfaction of the patient, which should include not only his state when he leaves the office but also after six months or a year's time.—HOWARD B. BURCHELL. *Cardiac Manifestations of Anxiety.* Proceedings of the Staff Meetings of the Mayo Clinic. Vol. 22, No. 20, October 1947.

Postvalvular Stenosis of the Pulmonary Artery

By C. Basil Williams, M.D., Ramon L. Lange, M.D., and Hans H. Hecht, M.D.

Constrictive lesions of the pulmonary artery or its branches occur distal to the pulmonic valve. Four patients whose surgical or cardiac catheterization findings demonstrated such postvalvular stenosis are reported. The significance of such findings is discussed and diagnostic misinterpretations are mentioned.

RECENT reports have focused attention on the occasional occurrence of localized constrictions in the pulmonary vascular system distal to the valve of the pulmonary artery. Such lesions have been called "coarctation of the pulmonary artery."[1-3] We believe the less specific term "postvalvular stenosis" to be somewhat more inclusive and more descriptive of these defects.

Schumacher and Lurie[4] have described a calcified stenotic lesion at the bifurcation of the pulmonary artery. This constriction was subsequently successfully dilated by spreading a Kelly clamp within the lumen of the artery. Sondergaard[1] has reported 3 cases of similar constrictions of the bifurcation encountered at surgery during a 3-year period. In each case, a fibrotic band, believed to be the ligamentum arteriosum, was attached to the constriction. Arvidsson, Karnell, and Möller[5] have demonstrated multiple stenotic lesions of the peripheral pulmonary vasculature in 4 patients by means of selective angiocardiography. Coles and Walker[3] have presented a case of "coarctation of the pulmonary artery" that was diagnosed by cardiac catheterization and angiocardiography. They also mentioned a case of Hodges that presented a similar picture. Recently, Eldridge, Selzer, and Hultgren[6] have reported 5 patients with stenosis of a branch of the pulmonary artery. In Bailey's text[2] is mentioned the existence of localized strictures of the main pulmonary artery termed "coarctation."

Since 1951 we have encountered 4 patients who apparently presented instances of this previously rarely reported anomaly.

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This investigation was supported in part by a grant from the Utah Heart Association, and the National Heart Institute, U. S. Public Health Service.

Case Reports

Case 1. G. E., a 15-year-old white boy, was first seen here in August 1951. At 2½ months gestation, his mother had rubella. At 20 months of age, deafness was discovered. His childhood was marked by slow development, easy fatigue, frequent upper respiratory infections, and exertional dyspnea. His nailbeds were always grayish. Orthopnea, edema, and squatting were never noted. Physical examination in 1951 revealed a small deaf mute with long digits and a prominent mandible. His heart was not enlarged to percussion. A brief systolic thrill and a harsh, loud systolic murmur with wide transmission were observed at the second and third left intercostal spaces along the left sternal border. The pulmonic second sound was louder than the aortic second sound. The remainder of the physical examination was unremarkable.

Cardiac fluoroscopy, x-ray films, and repeated electrocardiograms demonstrated right ventricular hypertrophy. The hemoglobin measured 16.8 Gm. per cent and the arterial oxygen content was normal at 20.4 volumes per cent (93 per cent saturated).

At cardiac catheterization, spot pressure readings revealed a right ventricular pressure of 64/0 mm. Hg. No "pull through" was obtained and no abnormal shunts were demonstrated. A diagnosis of pulmonary valvular stenosis was made but at surgery on September 8, 1952, a normal valve was discovered. The operative report stated: "The pulmonary valve was found to be approximately 25 per cent of normal size for the age and general size of the patient prior to dilatation and approximately 40 per cent postoperatively. The valve appeared normal in all respects. A diffuse low grade thrill was palpable over the pulmonary artery but not over the ventricle. A small urethral sound was inserted through the small incision and through the valve with no difficulty. A curved, flexible Bailey-Brock knife was then inserted through the incision and also passed through the valve with ease. The surgeon's finger was then likewise inserted and the valve was found to be essentially normal, but the artery was found to be markedly hypoplastic in its first part. A no. 34 uterine sound was then inserted into this hypoplastic artery segment with the resulting distinct increase in diameter of the artery."

When seen again in June 1953, the patient noted slight increased exercise tolerance, and less lethargy.

His murmur, thrill, and roentgenograms were unchanged.

Impression. A 15-year-old boy whose history and preoperative findings suggested valvular pulmonary stenosis. At surgery, a normal valve was present but a hypoplastic pulmonary artery segment was discovered and partially dilated.

Case 2. A. G., a white male infant, was 6 months old when first seen in April 1952 with a history of poor growth. A heart murmur had been present since birth. No cyanosis and no dyspnea had been observed. He had not been ill. Physical examination revealed a small infant with a loud blowing systolic murmur heard best in the third intercostal space along the left sternal border. The pulmonic second sound was decreased. The examination was otherwise unremarkable. At age 1½, he returned with the same findings. In addition, his parents noted that his lips became blue following exertion and that he seemed to tire easily. On August 27, 1953, a benign lymphangioma was removed from the right inguinal area. At that time an electrocardiogram suggested right ventricular hypertrophy. Cardiac fluoroscopy and x-ray films demonstrated the heart to be within normal limits.

On September 25, 1953, cardiac catheterization demonstrated no shunt or arterial desaturation, but did show a right ventricular pressure of 80/0 mm. Hg and a pulmonary artery pressure of 5/2 mm. Hg. He was observed over the next 2½ years during which time easy fatigue, circumoral cyanosis on exertion, occasional squatting, and frequent upper respiratory infections were noted.

On March 7, 1956, the patient, now 4 years old, was explored using a cardiac bypass technic.[7] At operation the interatrial septum was found intact. A stenotic pulmonary valve was found but, in addition, a marked narrowing of the pulmonary artery was observed 1½ cm. distal to the annulus (near the bifurcation). Following dilatation of the valvular stenosis, a right ventricular pressure of 100/0 and a pulmonary artery pressure of 50/18 were recorded while the patient was on the operating room table. Anesthetic difficulties precluded any further attempts to reduce this gradient, and the incision was closed. At the time of discharge on April 4, 1956, the systolic murmur was present as before. The patient moved away and has been lost to follow-up.

Impression. A 4-year-old boy with severe valvular pulmonary stenosis. In addition, a constriction of the pulmonary artery near the bifurcation was discovered at surgery.

Case 3. J. P., an 11-year-old girl, was seen here in June 1956 with the history that a heart murmur had been noted since age 3. Normal growth and development had occurred and cyanosis had never been observed. She was normally active but her mother noted she needed much sleep (particularly after exertion). She contracted frequent upper respiratory infections, but she had no known history of rheumatic fever or kidney disease. Physical examination revealed a healthy young girl with slight prominence of the left chest. Her heart was not enlarged to percussion. A systolic thrill was present along the left sternal border and a loud systolic murmur was heard over the entire precordium being loudest at the second left intercostal space. The pulmonic second sound was normal or slightly reduced.

Electrocardiograms, cardiac fluoroscopy, and x-ray films suggested right ventricular hypertrophy. The pulmonary artery segment was not prominent and there was no hilar dance. Cardiac catheteriza-

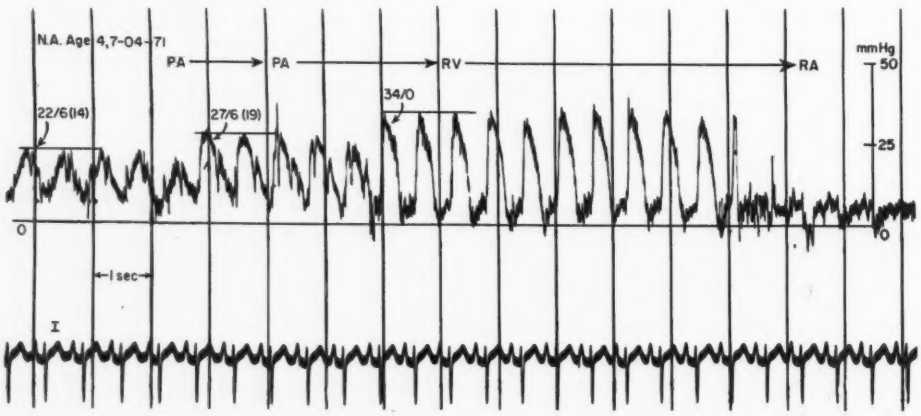

FIG. 1. Case 4. This pressure tracing was obtained by pulling the catheter from the distal pulmonary artery back across the pulmonary valve, through the right ventricle to the right atrium. Note the sharp increase in systolic pressure within the pulmonary artery and the additional rise at the pulmonary valve. Repeated "pull-through" tracings showed identical results.

tion and dye oximeter studies demonstrated a moderate left-to-right shunt through an interventricular septal defect. In addition, a stepwise pressure rise was observed in the pulmonary artery, rising abruptly from 26/11 mm. Hg (mean 19) to 33/11 mm. Hg (mean 22). An infundibular pressure was recorded at 33/0 mm. Hg and then rose abruptly again to 55/0 mm. Hg. The arterial oxygen saturation was 94 per cent.

Impression. An 11-year-old girl with an interventricular septal defect and infundibular pulmonary stenosis ("balanced" tetralogy of Fallot) and a postvalvular stenosis of the pulmonary artery.

Case 4. N. A., a 4-year-old white boy, was seen in November 1956. He presented a history of decreased exercise tolerance, rapid heart rate on exertion, and circumoral blueness when cold. A heart murmur had first been noted 1½ years previously. Physical examination revealed a well-developed boy of normal size for his age. Harrison's grooves were present bilaterally. The heart was enlarged to percussion. A systolic thrill was felt over the apex; a harsh holosystolic murmur and a short early diastolic murmur were heard over the same area and along the left sternal border. The pulmonic second sound was split but normal in intensity. Electrocardiograms demonstrated a prolonged P-R interval and an unusual rotation of the electric axis. Cardiac fluoroscopy revealed a globular heart with apparent right and left ventricular hypertrophy. Pulmonary markings and the pulmonary artery segment appeared normal.

Cardiac catheterization and oxygen sampling demonstrated interatrial and interventricular septal defects. The arterial oxygen saturation was 89 per cent. Several "pull-through" pressure tracings revealed a stepwise increase in pulmonary artery pressure from 22/6 mm. Hg (mean 14) to 27/6 mm. Hg (mean 19) with a further rise to 34/0 mm. Hg at the pulmonary valve (fig. 1).

Impression. A 4-year-old boy with interatrial and interventricular septal defects, slight valvular pulmonic stenosis ("pentology"), and a postvalvular stenosis of the pulmonary artery.

Discussion

Although infrequently reported, postvalvular stenosis ("coarctation") of the pulmonary artery is probably not rare. Sondergaard encountered 3 cases at surgery in as many years. We have seen 4 cases in 5 years, 2 of which were discovered at surgery and 2 by cardiac catheterization. A summary of the findings is presented in table 1. During this same period, we have seen a total of 70 patients with true pulmonary stenosis (valvular and infundibular) with or without associated defects.

It should be recognized that for a given flow a considerable degree of constriction must exist before a measurable pressure gradient in the pulmonary artery can be obtained. For example, a 50 per cent reduction in diameter will result in a 9 mm. Hg pressure drop across the constriction. Obviously minimal constriction may exist without demonstrable pressure changes (fig. 2). In view of these relationships, the case of Coles and Walker[3] is not clear-cut. Their pressure tracing is reminiscent of a "pull-out" from the "wedge" position to the pulmonary artery and then across a stenotic pulmonary valve. It seems unlikely that the degree of constriction they delineate with their angiocardiograms could cause the marked pressure changes they record by catheterization. On the other hand, when flow is raised, a pressure

Table 1.—*Findings in Four Cases of Postvalvular Pulmonary Stenosis*

	1 G. E.*	2 A. G.*	3 J. P.	4 N. A.
Sex and age (years)	M, 15	M, 4½	F, 11	M, 4
Height (inches)	61	38	56	41
Weight (pounds)	100	29½	78½	38
Pressures (mm. Hg)				
Distal pulmonary artery	31/0	5/2	26/11 (19)	22/6 (14)
Pulmonary artery trunk	—	—	33/11 (22)	27/6 (19)
Infundibular area	—	—	33/0	34/0
Right ventricle	64/0	80/0	55/0	34/0
Right atrium	—	2/0	12/1	
Associated defect				
Interatrial septal defect	0	0	0	+
Interventricular septal defect	0	0	+	+
Pulmonary stenosis (valvular)	0	+	0	+
Pulmonary stenosis (infundibular)	0	0	+	0
Arterial oxygen saturation (per cent) (Normal at Salt Lake City 91–94 per cent)	93	94	94	89

* Postvalvular stenosis found at surgery.

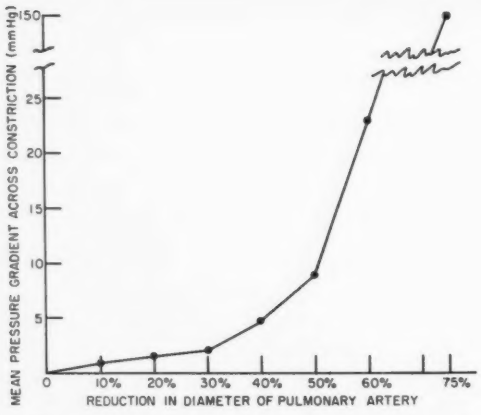

FIG. 2. This graph demonstrates the pressure gradient produced by various degrees of constriction within an inelastic tube. Pressure gradients were calculated using the energy equation

$$\frac{P_1}{w} + \frac{V_1^2}{2g} = \frac{P_2}{w} + \frac{V_2^2}{2g}$$

and solving for P_2, the pressure beyond the constriction.[8] We assume low frictional losses and neglect the coefficient of contractibility. P_1 is assumed to be a normal mean pulmonary artery pressure of 15 mm. Hg (20 cm. H_2O), and V_1 (velocity proximal to the constriction) is assumed to be 40 cm. per second.[9] Inasmuch as the velocity through the constricted area (V_2) varies inversely as the square of the radius, notice that after a critical amount of constriction is reached the pressure changes effected by constriction become most striking. If shunts are present and pulmonary flow is increased, constriction may produce more profound pressure changes. W = specific weight of blood. P measured in centimeters of water.

gradient may appear even if constriction is mild, a point clearly demonstrable in patients with mild stenosis of the mitral valve.

Certain other pitfalls exist in catheter diagnosis of these lesions. The case of Coles and Walker may point out one such error. When the catheter is pulled from the "wedge" position to the pulmonary artery, it is seen and felt to flip from its peripheral position and an abrupt increase in pressure is recorded (particularly if pulmonary hypertension is present). By sampling the oxygen content of the blood at both positions, the actual position can be determined, since either fully saturated blood or no sample at all will be obtained from the "wedge" position. Inadvertent "wedging" of the cardiac catheter and a spurious pressure rise must be ruled out before pulmonary constrictive lesions can be considered. Severe pulmonary stenosis per se may completely mask peripheral constriction (e.g., case 2), and such defects may be obvious only after the stenosis is relieved. Occasionally recordings taken near a patent ductus arteriosus may show a higher pressure than that recorded distally.[10] This might suggest postvalvular constriction but again judicious oxygen sampling and fluoroscopic examination of the catheter's position will aid in disclosing the true abnormality.

In any event, diagnosis of these lesions is important. Since various degrees of constriction may exist, they may or may not be functionally significant. Certainly marked involvement can mimic pulmonary stenosis very closely (e.g., case 1). The surgeon should be forewarned in such cases and should plan a more extensive procedure than a simple valvulotomy. Conversely, in cases of severe pulmonary stenosis, the surgeon should also search for distal constriction at the time of surgery since the 2 defects may coexist.

The etiology of these lesions is unknown; it is assumed that they are congenital in origin. The Skodaic theory[11, 12] (which emphasizes the obliteration of the ductus arteriosus as a causative factor) has been espoused by Sondergaard. However, it seems equally likely that multiple factors may cause these defects. Defective formation of the aortic septum must account for some cases. At least 5 of the 6 previously reported cases had coexisting pulmonary stenosis as did 3 of our 4 cases. This strongly suggests an association of the 2 defects.

SUMMARY

Four cases of postvalvular constrictions of the pulmonary artery are described. Such lesions may be isolated or associated with other defects, and may vary widely in their degree of severity. Certain pitfalls in diagnosis (misinterpretation of normal findings, or artifacts produced by a patent ductus arteriosus) are noted. The etiology is unknown but is assumed to be on a congenital basis. Such lesions are probably not so rare as the paucity of reports would indicate.

SUMMARIO IN INTERLINGUA

Es describite quatro casos de constriction postvalvular del arteria pulmonar. Tal lesiones occurre in isolation o in association con altere defectos. Illos varia grandemente in grado e severitate. Certe riscos diagnostic es signalate que resulta in le misinterpretation de conditiones normal o de artefactos producite per un patente ducto arteriose. Le etiologia non es cognoscite sed pare haber un base congenite. Lesiones de iste genere es probabilemente minus rar que lo que es indicate per le paucitate de reportos.

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Using rigid criteria for the diagnosis of hypertension the authors examined the records of 509 patients under treatment for malignant neoplasms to determine the incidence of hypertensive disease in such a group. A similar number of control patients without neoplasms, matched for distribution of sex and age were included in the study. It was found that in both sexes and all ages, essential hypertension was less common in the neoplastic than in the control group. The difference was more striking in men than in women. These observations are in agreement with previous studies in which less rigid criteria for hypertension were applied. If the reference standard used is a working population in which the incidences of hypertension are 9 per cent in men and 10 per cent in women, the observed values of 1 per cent and 6 per cent respectively in the neoplastic cases may have further significance. It is suggested that a broad epidemiologic and experimental study is needed to evaluate the dissociation between hypertension and neoplastic disease.

SHUMAN

Effect of *Rauwolfia serpentina* and Reserpine on the Blood Pressure in Essential Hypertension

A Long-Term Double-Blind Study

By MURRAY B. SHELDON, M.D., AND J. HAROLD KOTTE, M.D.

A 2-year double-blind study of 18 ambulatory patients treated with *Rauwolfia serpentina* and reserpine is presented, with a statistical evaluation by the method of analysis of variance.

SINCE 1951, the American literature has become replete with reports of the blood pressure-reducing effects of *Rauwolfia serpentina* and its derivatives in the management of essential and other varieties of hypertensive disease.[1-11] The initial interest was stimulated by a report of Vakil in 1949,[12] though other favorable reports in the Indian literature appeared as early as 1940.[13, 14] Since optimistic papers in the American literature insured widespread use of these drugs, it is apparent that they merit a thoroughly objective appraisal. The present double-blind study was undertaken with this purpose in mind.

METHOD

The Double-Blind Technic

A long-term double-blind study of any pharmacologic agent is handicapped by the attitude of the clinician as well as by the therapeutic and side effects of the drug under investigation. These drawbacks often preclude the use of a given drug for this type of study, primarily because of obvious hazards due to individual patient susceptibility; this necessitates careful individualization of dosage to achieve a desirable therapeutic effect without producing potentially dangerous side effects. Most of the newer hypotensive drugs fall into such a category and therefore cannot be safely evaluated with the double-blind technic. *Rauwolfia serpentina* and its derivatives are unique in this respect in that clinical experience has indicated that there is a mean dose applicable to most patients, that blood pressure reduction is modest in degree and never striking, and that serious side effects are quite rare. The attitude of the investigator, working with the double-blind technic in such an atmosphere, is, therefore, more likely to be objective.

From the Cardiac Laboratory and the Hypertension Clinic of the University of Cincinnati College of Medicine and Cincinnati General Hospital, Cincinnati, Ohio.

Even with rauwolfia and derivatives there are certain side effects that may serve as a signal that the active drug is being administered. Bradycardia is common and is the most likely clue. Occasionally diarrhea, nausea, somnolence, fatigue, nasal stuffiness, and depression are seen. Whether these side effects invalidate the double-blind is a moot question. If so, there is no method, to our knowledge, to circumvent them, short of introducing other drugs that may also affect the blood pressure.

Patients

Observations were made on 28 patients with essential hypertension seen weekly or biweekly in the Hypertension Clinic of the Cincinnati General Hospital. The study was carried out over a 2-year period ending in August 1954. Of the 28 patients, sufficient data are available in 18 to allow for adequate statistical evaluation. Of the 18, 17 were Negroes and 13 were women. The ages of the patients ranged from 40 to 56 years, with a mean of 47 years. Duration of known hypertension prior to the study varied from 1 to 29 years with a mean of 3.6 years. All patients were followed for at least 4 consecutive weeks prior to the institution of the study, during which period they received no specific blood pressure-reducing medication, although some patients had received hypotensive drugs previously. During the study, essential measures, such as digitalis, salt restriction, and mercurial diuretics were continued when appropriate. No patient was studied in whom the blood pressure had not remained stable for 4 to 6 consecutive weeks. Each patient was followed by a single clinician and in many instances a firm doctor-patient relationship antedated the study by several months.

All 18 patients had a diagnosis of essential hypertension. The optic fundi were grade II in 15 and grade III in 3. Seven patients had a history of congestive heart failure controlled by appropriate treatment, 4 had previous cerebral thrombosis or hypertensive encephalopathy, and 2 had a history of urinary tract infection in the past with some impairment of renal function but without urea retention. In these 2 patients, primary renal hypertension could not be ruled out. In 7 patients, systolic blood pressure had been consistently over 200 mm. Hg,

and in 6 the diastolic blood pressures had been consistently over 120 mm. Hg. At one time or another prior to the study 14 patients had received treatment with one or more of the following drugs or combinations thereof: phenobarbital, hexamethonium, hydralazine, veratrum compounds, *Rauwolfia serpentina*, low-sodium diet. With the exception of a favorable result in 1 patient who received phenobarbital, the eventual responsiveness to these agents was clinically unsatisfactory. Two of the 9 patients who had been tested with tetraethyl ammonium chloride intravenously, usually in a dose of 4 ml., had excellent depressor responses.

Drug Administration

The double-blind schedule was planned by a physician not concerned with the study. He was instructed to establish schedules in such a way that a given patient would receive alternate courses of placebo and a depressor drug for 6 or more weeks. The purpose of administration of alternate courses of placebo and a depressor drug was 2-fold: first, to nullify as far as possible any error due to spontaneous changes in blood pressure during the period of study, and, second, to minimize guesswork on the part of clinicians. Schedules were made in advance of the study and assigned in order as each new patient entered the project. Tablets were dispensed in sealed envelopes containing a 1 or 2 weeks' supply. This made it possible for clinicians to chart omitted doses.

Patients in the study were notified at the start that they were to receive a new medicine under investigation for blood pressure control. They were not advised that they might receive a placebo. They were indoctrinated in the importance of weekly visits and taking all medication as directed. Potential side effects were not suggested except for a short period later in the study when the effect of an antihistamine, pyrrobutamine, on reserpine-induced nasal stuffiness was investigated. Although the antihistamine appeared to exert a slight salutary effect on this symptom and had no demonstrable effect on blood pressure, nasal stuffiness was inadvertently induced by suggestion in 11 of 15 patients receiving placebo at the time.

Clinicians were aware of the double-blind plan only to the extent that they knew that a given patient would receive alternate courses of drug and placebo of variable duration.

No formal attempt was made to ascertain when patients were receiving drugs or placebo. Regular weekly examinations, as in the pre-study period, consisted of a routine interval medical history and physical examination with the usual emphasis on the cardiovascular system including the optic fundi. Blood pressure readings were taken by the clinician in a quiet examining room and in most instances at the same time of day and at the same time interval after a dose of medication. Two or more readings were made after 15 to 20 minutes each in the supine, seated, and standing positions. Periodic laboratory examinations were made including urinalysis, phenolsulfonphthalein test, urine concentration test, blood urea nitrogen, electrocardiogram, chest x-ray, and blood count. None of these changed appreciably during the course of the study.

During the first 3 months of the study either the crude root of *Rauwolfia serpentina* or an identical lactose placebo was administered. The dose of *Rauwolfia serpentina* was 50 mg. 4 times daily. Thereafter, throughout the remainder of the study either reserpine, 0.2 mg. and later 0.25 mg., or an identical lactose placebo was administered on the same schedule.

Analysis of Data

The systolic and diastolic blood pressures of each patient were studied separately by the technic of analysis of variance. (This general technic is briefly illustrated in the appendix for 1 patient, C. E.). F_1 values were obtained to determine whether any significant difference existed between the blood pressure readings recorded when the patient was receiving the drug and those recorded when he was receiving either a placebo or no medication. Similarly the F_2 test was used to determine whether a significant difference existed between pressures taken during the period of placebo administration and pressures taken during the relatively brief period when no medication was taken. If the F_2 test indicated a probability of less than 5 per cent, a comparison was also made between pressures taken during the administration of the drug and those recorded during the administration of the placebo. Otherwise the short periods when no medication was administered were included with the periods of placebo administration in the F_1 test. The entire statistical analysis was carried out in such a way that the degree of probability of either the drug or of the placebo having a postural effect could also be determined by applying appropriate F tests for interaction (designated as F_3 and F_4 respectively in the appendix).

With this method results are expressed as follows, according to chance probabilities: (*) barely significant (p greater than 1 per cent but less than 5 per cent); (†) significant (p greater than 0.1 per cent but less than 1 per cent); (‡) highly significant (p less than 0.1 per cent.)

Results

In table 1 are given the results of a statistical analysis of the blood pressure readings during periods of *Rauwolfia serpentina* and reserpine administration and during periods of placebo or no medication. The results of the statistical analysis of the blood pressure read-

TABLE 1.—*Statistical Analysis with Blood Pressure Readings during Administration of Rauwolfia*

A. Mean systolic blood pressures

Patient	Age	Sex	Race	*Rauwolfia serpentina* or reserpine	Placebo or no medication	F
Group 1						
M. Mi	53	F	N	220	233	32.7‡
J. S.	40	F	N	200	221	30.2‡
R. L.	50	F	N	182	200	23.0‡
A. M.	42	M	N	169	188	18.3‡
C. E.	51	F	N	194	208	13.7‡
E. R.	40	F	N	157	170 (164)	12.8‡ (2.7)
M. Ma.	56	F	N	184	194	7.9†
R. S.	40	F	N	198	207	6.8*
Group means				188.0	202.6 (201.9)	
Group 2						
C. J.	42	F	N	191	201	3.7
D. E.	56	F	N	175	182	2.9
J. B.	44	M	N	176	184	2.3
E. B.	53	F	N	226	232	1.7
L. C.	47	M	W	146	151	1.5
W. T.	53	M	N	227	229 (227)	0.5
F. H.	49	F	N	214	214	0.0
Group means				193.6	199.0 (198.7)	
Group 3						
S. B.	47	F	N	207	194	4.3*
B. B.	40	F	N	186	178	7.5†
T. B.	48	M	N	209	193	12.9‡
Group means				200.7	188.3	
Grand means				192.3	198.8 (198.4)	

B. Mean diastolic blood pressures

Patient	Age	Sex	Race	*Rauwolfia serpentina* or reserpine	Placebo or no medication	F
Group 1						
M. Mi	53	F	N	128	141 (140)	93.7‡ (42.2‡)
R. L.	50	F	N	104	118	50.7‡
J. S.	40	F	N	108	125 (123)	45.0‡ (20.6‡)
A. M.	42	M	N	116	137	44.5‡
M. Ma.	56	F	N	88	98 (96)	35.1‡ (20.8‡)
C. E.	51	F	N	115	124	25.2‡
E. R.	40	F	N	99	107 (103)	15.3‡ (3.7)
B. B.	40	F	N	117	126	14.9‡
R. S.	40	F	N	125	133	13.0‡
D. E.	56	F	N	105	112	9.9†
W. T.	53	M	N	129	134	7.3†
Group means				112.2	123.2 (122.7)	
Group 2						
J. B.	44	M	N	105	114	4.1
L. C.	47	M	W	99	103	1.7
C. J.	42	F	N	122	125 (129)	0.8 (3.1)
F. H.	49	F	N	116	118	0.8
E. B.	53	F	N	136	138	0.5
S. B.	47	F	N	124	124	0.0
Group means				117.0	120.3 (121.0)	
Group 3						
T. B.	48	M	N	145	136	8.5‡
Grand means				115.6	122.9 (122.7)	

The mean systolic and diastolic blood pressures of each patient recorded during periods of administration of *Rauwolfia serpentina* or reserpine are compared with similar mean pressures obtained during periods of administration of a placebo or of no medication. The patients are arranged in serial order according to the F values. Group 1 consists of those patients in which the administration of *Rauwolfia serpentina* or reserpine is associated with a statistically significant fall in pressure. Group 2 consists of those patients in whom there is no significant difference between the levels of blood pressure obtained when one of these drugs was given and when a placebo or no medication was administered. In group 3 the administration of *Rauwolfia serpentina* or reserpine was associated with a significantly higher level of blood pressure. The blood pressures given in parentheses refer to mean pressures obtained when patients were receiving the placebo. These are listed separately only in those patients in whom the administration of a placebo as opposed to no medication is associated with a significant difference in mean blood pressure (see table 2). In such instances separate F tests, utilizing the mean pressures obtained during placebo administration, are also given in parentheses.

* Barely significant (p greater than 1 per cent but less than 5 per cent).

† Significant (p greater than 0.1 per cent but less than 1 per cent).

‡ Highly significant (p less than 0.1 per cent).

ings during periods of placebo administration and during periods of no medication are listed in table 2. Data relating to the systolic pressures are given in part *A* and those relating to the diastolic pressures are listed in part *B* of each table.

Table 1 indicates that, for the systolic blood pressure, 8 of the 18 patients had a significant blood pressure-lowering effect with the drug as compared to the readings obtained with the placebo or no medication. However, 1 of these 8 patients, E. H., had a marked drop in systolic blood pressure with the placebo and no significant difference between pressures recorded during drug administration and placebo administration. Three of the 20 patients had significantly higher blood pressures while on the drug than on the placebo.

In the case of the diastolic blood pressure, table 1 indicates that 11 of the 18 patients had significantly lower pressures while receiving rauwolfia or reserpine than while receiving placebo or no medication. Again 1 patient, E. R., must be eliminated from this group of 11

TABLE 2.—*Statistical Analysis with Blood Pressure Readings during Periods without Rauwolfia*

A. Mean systolic blood pressures

Patient	Age	Sex	Race	Placebo	No medication	F
Group 1						
E. R.	40	F	N	164	192	23.2‡
W. T.	53	M	N	227	239	9.1†
Group means				195.5	215.5	
Group 2						
B. B.	40	F	N	175	182	3.4
M. Mi.	53	F	N	232	239	3.3
J. S.	40	F	N	220	226	1.5
S. B.	47	F	N	192	198	1.1
T. B.	42	M	N	192	196	0.8
F. H.	49	F	N	212	217	0.4
E. B.	53	F	N	231	236	0.4
J. B.	44	M	N	182	186	0.4
D. E.	56	F	N	182	184	0.2
R. S.	40	F	N	207	209	0.1
C. E.	51	F	N	208	207	0.0
R. L.	50	F	N	200	199	0.0
L. C.	47	M	W	152	150	0.1
A. M.	42	M	N	189	186	0.2
M. Ma.	56	F	N	195	188	1.6
C. J.	42	F	N	206	195	2.5
Group means				198.4	199.9	
Grand means				198.1	201.6	

B. Mean diastolic blood pressures

Patient	Age	Sex	Race	Placebo	No medication	F
Group 1						
E. R.	40	F	N	103	119	29.6‡
M. Mi.	53	F	N	140	146	7.6†
J. S.	40	F	N	123	131	7.4†
M. Ma.	56	F	N	96	103	5.4*
Group means				115.5	124.8	
Group 2						
W. T.	53	M	N	133	138	3.3
F. H.	49	F	N	117	122	2.8
B. B.	40	F	N	123	129	2.5
D. E.	56	F	N	111	114	1.2
E. B.	53	F	N	137	142	0.9
J. B.	44	M	N	112	116	0.6
T. B.	48	M	N	136	137	0.1
S. B.	47	F	N	124	125	0.1
A. M.	42	M	N	137	137	0.0
R. S.	40	F	N	133	133	0.0
L. C.	47	M	W	103	101	0.5
R. L.	50	F	N	119	114	2.3
C. E.	51	F	N	125	119	3.3
Group means				123.8	125.2	
Group 3						
C. J.	42	F	N	129	120	5.0*
Grand means				122.3	124.8	

The mean systolic and diastolic blood pressures of each patient recorded during periods of administration of the placebo are compared with similar mean pressures obtained when no medication was given. The division of the patients into groups is entirely analogous to the arrangement of table 1.

* Barely significant (p greater than 1 per cent but less than 5 per cent).

† Significant (p greater than 0.1 per cent but less than 1 per cent).

‡ Highly significant (p less than 0.1 per cent).

cases in that the blood pressures dropped significantly with the placebo and were not significantly different from those recorded with the drug. One of the 18 patients, T. B., had significantly higher pressures while receiving rauwolfia or reserpine than when receiving placebo or no medication.

Table 2 demonstrates that the placebo was associated with a significant lowering of the systolic blood pressure in 2 of the 18 patients and of the diastolic blood pressure in 4 of the 18 patients. In 1 patient, C. J., a significantly increased diastolic pressure was obtained with the placebo.

In only 1 patient was there a barely significant postural effect of the drug on systolic pressure and in another patient a barely significant postural effect of the drug on diastolic blood pressure. In these 2 instances the blood pressure progressively fell as the patient changed from the reclining to the sitting and to the standing positions. In all other patients the F_3 and F_4 values did not approach statistical significance.

Statistically significant responsiveness in the study could not be correlated with duration of known hypertension, the presence or history of cardiovascular, renal, or cerebral complications, age of patients, or responsiveness to other blood pressure-reducing drugs previously administered. Responsiveness to the tetraethyl

ammonium chloride test was, in general, associated with unresponsiveness to rauwolfia and derivatives although the data are insufficient to permit definite conclusions.

Discussion

Although a statistically significant lowering of systolic and diastolic blood pressures by *Rauwolfia serpentina* and reserpine was frequently observed during this study, one point deserves emphasis. In the patients studied, reduction of blood pressures by 10 to 15 mm. Hg on the drug often assumed statistical significance of high order. While a significant pharmacologic effect was demonstrated in these instances, this effect was not necessarily a significant one from a clinical standpoint. For example, reductions in mean systolic blood pressure readings from 203 to 188 (first group of table 1*A*) and reductions in mean diastolic blood pressure readings from 123 to 112 (first group of table 1*B*), although statistically significant, have doubtful therapeutic implications.

The individual blood pressure records of these patients whose response to depressor drugs was statistically significant revealed that time was not a determining factor. Although the mean systolic and diastolic blood pressures were reduced during the periods of drug administration, individual blood pressure readings were variable during the period and were unrelated to the duration of administration of the drug. The placebo periods revealed a similar variability of individual blood pressure readings unrelated to time. These observations were consistent throughout the study regardless of whether a patient commenced on drug or placebo and suggest that there is neither a time lag in depressor effect of *Rauwolfia serpentina* and reserpine nor a carryover effect when they are discontinued. For this reason, all blood pressure readings were included in the statistical analysis.

In no case was there any serious untoward reaction during therapy. Bradycardia was usually present. There were no gastroenteric symptoms that could be attributed to therapy. Although drowsiness, malaise, and decreased tension were observed in some cases, no instance of severe mood changes were noted. The authors have occasionally observed moderately severe mental depression with similar doses in other patients not reported here. There were no significant changes in the optic fundi. There were no instances of weight gain, edema, or precipitation of congestive heart failure as reported elsewhere,[15, 16] although these have sometimes occurred with dosage in excess of that used here.

"The powerful placebo," as Beecher chose to call it,[17] can be made to modify many autonomic reactions, including a lowering of the blood pressure. In the present study a statistically significant lowering of systolic and diastolic blood pressures by placebo when compared to no medication was found in 2 and 4 patients respectively. Obviously no drug, no matter how potent or inert it may be pharmacologically, is devoid of a variable and often incalculable placebo effect.[18-20] No one would question the fact that this represents a therapeutic advantage provided the effect is positive rather than negative. Evidence suggestive of such a negative effect is seen in the present study in that the systolic pressure in 3 patients and the diastolic pressure in 1 patient were significantly higher on *Rauwolfia serpentina* and reserpine than on placebo and no medication. However, it is necessary that the placebo effect, whether it be positive or negative, be effectively neutralized if one is to determine the pure pharmacologic effectiveness of any agent. This is particularly true in hypertension where blood pressure fluctuations of the magnitude induced by *Rauwolfia serpentina* and its derivatives are known to occur as a result of emotional factors alone.[21, 22]

Rauwolfia serpentina and its derivatives can and should be tested for pharmacologic effectiveness by the double-blind technic over a long period to neutralize, as far as possible, the factors of the enthusiasm of the patient and the physician, as well as transient or intermittent emotional problems, before conclusions are drawn concerning its mode of blood pressure reduction.

Summary

A 2-year double-blind study of 18 ambulatory patients treated with *Rauwolfia serpentina* and reserpine is presented.

A statistical study, utilizing analysis of variance, revealed a significant depressor effect of *Rauwolfia serpentina* and its derivatives over placebo on the systolic pressure in 7 of 18 patients and on the diastolic pressure in 10 of 18 patients. A significant placebo effect on the systolic and diastolic pressures occurred in 2 and 4 of the 18 patients, respectively. Statistically significant responses were in the range of 9 to 21 mm. Hg, systolic, and 7 to 15 mm. Hg, diastolic. Therefore, they were not necessarily significant clinically.

Acknowledgment

The authors wish to express their appreciation to Dr. Johnson McGuire, Director of the Cardiac Laboratory, and to Dr. Ralph C. Scott, for advice in the organization of the study, and to Drs. Isom Walker, William Stiles, and James Evans, as participating clinicians. Mr. Harold Perlman and Miss Daphne Anderson calculated the statistical results. Dr. Robert Helm supervised the statistical analysis and was a participating clinician. Mrs. Elizabeth Wise prepared the manuscript.

The *Rauwolfia serpentina* used in this study was supplied by E. R. Squibb and Sons, New York, New York, and the reserpine by Eli Lilly and Company, Indianapolis, Ind.

Addendum

During the preparation of this report 2 double-blind studies have been reported with *Rauwolfia serpentina* and reserpine over a 4- and 6-month period[23, 24] with a statistical analysis of the blood pressure changes in the latter that are, in general, in agreement, with ours. We are unable to find any similar long-term double-blind studies in our review of the literature.

Summario in Interlingua

Es presentate un bienne studio bis-occulte de 18 patientes ambulatori qui esseva tractate con Rauwolfia serpentina e reserpina.

Un studio statistic (basate super le analyse del quadrate deviationes standard) revelava un significative effecto depressori de Rauwolfia e su derivatos super le pression systolic in 7 ex le 18 patientes e super le pression diastolic in 10. Un effecto significative super le pressiones systolic e diastolic occurreva in 2 e 4 patientes, respectivemente, post medication fictitie. Le statisticamente significative responsas variava inter 9 e 21 mm Hg systolic e inter 7 e 15 mm Hg diastolic. Per consequente, illos non esseva necessarimente de signification clinic.

Appendix

The following is an abbreviated example of an analysis of variance of 102 systolic blood pressure readings recorded on patient, C. E., in the reclining, sitting, and standing positions during periods of administration of drug, placebo, and no medication.

Source of variation	Degrees of freedom	Sum of squares	Mean square
Treatments			
Drugs vs. placebo and no medication	1	4,794.71	4,794.71
Placebo vs. no medication	1	7.45	7.45
Positions	2	5,139.24	2,569.62
Interactions			
Drug vs. placebo and no medication, with positions	2	90.84	45.42
Placebo vs. no medication, with positions	2	46.12	23.06
Discrepancy within subclasses	93	32,512.45	349.60
Totals	101	42,590.81	

Tests of null hypotheses

Treatments	
Drug vs. placebo and no medication	$F_1 = \frac{4,794.71}{349.60} = 13.72‡$
Placebo vs. no medication	$F_2 = \frac{7.45}{349.60} = 0.02$
Interactions	
Drug vs. placebo and no medication, with positions	$F_3 = \frac{45.42}{349.60} = 0.13$
Placebo vs. no medication with positions	$F_4 = \frac{23.06}{349.60} = 0.07$

‡ Highly significant (p less than 0.1 per cent).

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Dance, C. L., Boozer, J., Newman, W., and Burstein, C. L.: Electrocardiographic Studies during Endotracheal Intubation: VII. Evipal Sodium Induction. Anesthesiology **17:** 730 (Sept.–Oct.), 1956.

The authors report electrocardiographic studies in 119 adult patients in whom anesthesia was induced with intravenous Evipal sodium. The most frequent change noted was an increase in the cardiac rate of about 20 beats per minute. No harmful effect was observed with Evipal sodium, even in those patients who previously had abnormal hearts and electrocardiograms. The use of Evipal sodium with cyclopropane or ether for intubation appeared to afford some protective action against the precipitation of cardiac arrhythmias because comparison with a similar series showed only a 1 per cent incidence of cardiac arrhythmias on intubation with Evipal sodium and an incidence of 28 per cent without Evipal sodium.

SAGALL

Clinicopathologic Correlations of Renal Biopsies from Essential Hypertensive Patients

By Myron Saltz, M.D., Sheldon C. Sommers, M.D., and Reginald H. Smithwick, M.D.

The pathologic findings of kidney biopsies in an extensive series of patients undergoing sympathectomy are reported. The findings are correlated with the clinical status, level of hypertension, postoperative course, and length of survival.

RENAL tissue was obtained by biopsy from 1,251 hypertensive patients who underwent sympathectomy[1] at Massachusetts Memorial Hospitals in the 10 years 1946 through 1955. A clinicopathologic correlation has been attempted on the basis of a pathologic analysis of approximately 1,700 specimens and of 305 case histories.

The purpose of the present study is to determine how accurate an estimation may be made of the clinical status, level of hypertension, renal function, response to sympathectomy, and probable course of essential hypertension by histologic examination of a small portion of kidney tissue; some comparison of the relative value of different individual tests in hypertension is also possible.

Materials and Methods

The renal biopsies were about 6 by 5 by 4 mm., were almost exclusively composed of kidney cortex, and were removed as described by Castleman and Smithwick.[2] In 348 patients, bilateral biopsies were removed; 6 patients had 3 biopsies.

Pathologic alterations of the glomeruli, juxtaglomerular apparatus, tubules, stroma, and blood vessels were recorded for each specimen, without knowledge of the patient's identity or status. The morphologic observations are presented elsewhere, but for the present purpose all recognized diseases other than arteriolar nephrosclerosis have been excluded, except as specifically mentioned. Grading of abnormalities of the small arterioles was based upon the degree of thickening of their walls, at the expense of the lumen. *Negative* arterioles showed no evident alteration, grade I arteriolar sclerosis indicated minor localized thickenings of the walls, grade II change referred to a thickened wall equal to the diameter of the lumen, and grade III sclerosis meant that the wall thickness exceeded the diameter of the lumen. The grade recorded was the estimated average arteriolar thickening throughout the specimen.

Vascular necrosis was separately recorded as generalized or focal. Most of the latter lesions accompanied grade II arteriolar sclerosis. Clinicopathologic analysis of 40 such cases showed no significant distinctions from similar kidneys lacking focal vascular necrosis. For the clinical analyses, all available cases of the less common grades were reviewed, as well as 100 consecutive cases of the more common grades operated on in 1946 and subsequent years. Two cases of pyelonephritis were included in the group with grade III arteriolar sclerosis and vascular necrosis.

Results

Pathologic Observations. In table 1 are summarized the diagnoses for the entire series. It is evident, as found also by others,[3-6] that severe renal vascular disease was uncommon, (5.0 per cent of the total cases) while moderate or slight arteriolar sclerosis predominated (93.7 per cent) in these persons with essential hypertension. On the bases of these cases and the occasional ones without any pathologic change (1.1 per cent) structural alterations of renal arterioles evidently do not constitute the etiologic basis of essential hypertension.

Vascular necrosis of the diffuse fibrinoid type occurred in 25 cases; 18 with grade III and 7 with grade II arteriolar sclerosis. Necrosis was thus not a complication only of the most advanced arteriolar disease, nor was it purely a terminal finding. In previous series the incidences reported varied from 0 of 600 biopsies[2, 4] to 13 of 50 cases.[3] Schottstaedt and Sokolow[7] found 4 cases with necrosis among 35 autopsied instances of clinically malignant hypertension with papilledema.

Pyelonephritis, as Heptinstall[3] indicated, is

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TABLE 1.—*Pathologic Diagnoses of Kidney Biopsies from 1,251 Hypertensive Patients*

	Single biopsies	Multiple biopsies
Cases	897	354
Negative kidney	14 (1.6%)	0
Arteriolar sclerosis, total	738 (82.4%)	291 (82.2%)
Grade I	220 (24.6%)	42 (11.8%)
Grade II	481 (53.7%)	232 (65.6%)
Grade III	37 (4.1%)	17 (4.8%)
Vascular necrosis	11 (1.2%)	14 (4.0%)
Pyelonephritis	119 (13.3%)	49 (13.8%)
Glomerulonephritis	5 (0.6%)	4 (1.1%)

TABLE 2.—*Relation of Age and Sex to Severity of Arteriolar Nephrosclerosis in Essential Hypertension*

Age (years)	10–39	40–59	Male	Female
Kidney, 18 negative	8	10	6	12
100 grade I	36	64	33	67
100 grade II	32	68	50	50
29 grade III	6	23	19	10
18 grade III and vascular necrosis	6	12	10	8
Total			44.5%	55.5%

not accurately diagnosed by renal cortical biopsies; the low over-all incidence of 13.4 per cent may be due to the technic employed. The acute, chronic, and healed stages were pooled in the present study. While separate consideration of the relation of pyelonephritis to hypertension is planned, it was concluded that in this series the severity of arteriolar sclerosis was not significantly altered by the presence of pyelonephritic inflammation.

Comparison of diagnoses of the 346 graded bilateral biopsies, examined as unknowns, revealed the same grade in 60.7 per cent and a difference of one grade in 38.7 per cent. Castleman and Smithwick[4] reported the same grade bilaterally in 75 per cent of their cases. The intervals between multiple biopsies were from 8 days to 3 weeks. No consistent differences were found between the first and second biopsies.

Clinical Information. As shown in table 2, age tended to be greater in the groups with more severe arteriolar nephrosclerosis. Striking examples of this have been reported.[3, 4] A

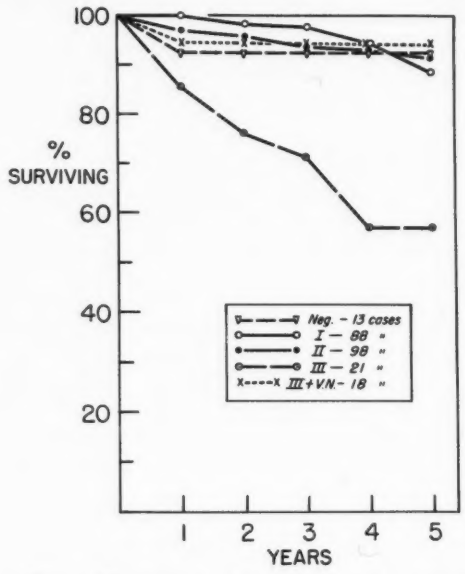

FIG. 1. Five-year survivals among various renal vascular grades.

majority of male patients were within the groups with advanced vascular disease.

Survival at a 5-year postoperative interval for each grade of arteriolar nephrosclerosis is recorded in figure 1. Except for grade III arteriolar sclerosis, which was more common in older persons and pathologically more diffuse as well as of extreme degree, there were no significant group differences in the survivals after operation. All other groups had high survival rates, including those with vascular necrosis. In patients treated by sympathectomy no graver prognosis was associated with diffuse vascular necrosis, contrary to previous impressions from study of autopsy material.

Diastolic blood pressure levels, defined as the lowest values obtained in the recumbent patients, were found to be elevated corresponding to the independently assayed histologic grade of arteriolar sclerosis. With negative kidney biopsies the mean preoperative diastolic level was 100 mm. Hg; with grade I arteriolar sclerosis it was 103; grade II, 109; grade III, 122; grade III with vascular necrosis, 117. By Student's t test the mean diastolic values differed significantly between grade I, II, and III ($p \leqq 0.05$).

It was of interest that the mean diastolic blood pressure level with grade III arteriolar sclerosis and vascular necrosis was below the 130 mm. Hg thought requisite by Heptinstall[8] and Pickering[9] for development of this lesion. Focal necrosis was observed at considerably lower pressure levels. No case with diffuse vascular necrosis showed azotemia.

Postsympathectomy responses of blood pressure have been graded as follows according to criteria previously devised.[10, 11]

Postoperative reductions of diastolic blood pressure were: grade 1, 20 or more mm., and below 90 mm.; grade 2, 20 or more mm., and below 110 mm.; grade 3, 10 to 19 mm., and below 110 mm.; grade 4, 10 to 19 mm., not below 110 mm.; grade 5, no change, plus or minus 9 mm.; grade 6, none, increase of 10 mm. or more. Among the 77.4 per cent of the total 305 cases successfully followed medically for 5 years, the best over-all responses of blood pressure were among those with grade III arteriolar sclerosis with or without vascular necrosis, since, of these, 46 per cent and 59 per cent respectively fell into grades 1 to 3. Approximately one third of those with negative kidneys or grades I or II arteriolar sclerosis showed blood pressure reductions of grades 1 to 3. Heptinstall[3] likewise has reported substantially reduced blood pressure levels after sympathectomy in hypertension with advanced nephrosclerosis.

Retinal grading of vascular changes (Keith-Wagener) was compared with the renal histology, and the postoperative improvement in eyegrounds was analyzed. Hypertensive retinitis was not frequently severe in the entire series, since 76.7 per cent of the cases analyzed had retinal grades 0, I, and II. No definite correlation was found between the degrees of vascular change in the retina and kidney. More severe retinal changes were concentrated in older age groups, as expected. Grade IV retinitis occurred with grades I, II, and III arteriolar nephrosclerosis, but was not observed with renal vascular necrosis. More specific criteria for hypertensive retinopathy are desirable, as Minsky[12] suggested.

After sympathectomy 48.6 per cent of the cases analyzed showed improvement in the appearance of the eyegrounds, without apparent relation to the different grades of arteriolar nephrosclerosis. Few abnormal eyegrounds returned to normal after sympathectomy (13.0 per cent).

Renal function, as measured by the phenolsulfonphthalein excretion, was compared before and after sympathectomy on the basis of the last available follow-up test, 1 to 9 years after operation (table 3). Impaired phenolsulfonphthalein excretion was judged as slight when less than 25 per cent dye was excreted in 15 minutes, or below 60 per cent in 2 hours; as moderate, when less than 20 per cent was excreted in 15 minutes; or marked, when less than 15 per cent was excreted in 15 minutes.

A tendency was found to decreased phenolsulfonphthalein excretion with more severe and

TABLE 3.—*Phenolsulfonphthalein Excretion Tests before and after Operation, Compared with Renal Vascular Alterations*

	Preoperation				Postoperation		
	Normal	Impaired			Same	Improved	Worse
		Sl.	Mod.	Mkd.			
Kidney biopsy							
18 negative	83%	11%	0%	6%	0%	100%	0%
Arteriolar sclerosis							
100 grade I	68	24	6	2	7	82	11
100 grade II	63	25	7	5	6	74	19
29 grade III	69	17	10	3	20	80	0
18 grade III and vascular necrosis	56	33	11	0	17	33	50
Totals	64%	36%			10%	74%	16%

extensive arteriolar nephrosclerosis. At the extremes, 83 per cent of the hypertensive persons with histologically negative kidney biopsies had normal phenolsulfonphthalein tests, in contrast to 56 per cent of those with severe arteriolar sclerosis and diffuse vascular necrosis. After sympathectomy this latter group had the least improvement of phenolsulfonphthalein excretion (33 per cent) and most commonly showed progressive impairment postoperatively (50 per cent). Among the intermediate grades of arteriolar sclerosis no significant differences in phenolsulfonphthalein excretion were evident.

Values of serum nonprotein nitrogen exceeding 40 mg. per 100 ml. were found in only 3 of the 305 cases preoperatively. One showed a negative kidney biopsy and the others were of grades I and III nephrosclerosis. All had normal phenolsulfonphthalein tests. Postoperatively all of the nonprotein nitrogen determinations were normal, and only the last case mentioned had subsequently impaired phenolsulfonphthalein excretion.

Clinical grouping of hypertensive patients, in terms of age, cerebral, cardiac and renal disease, eyeground changes, and response to sedation have been employed for previous analyses.[10, 11] Among the 6 so-called Smithwick groups, an increased severity is accorded a higher group number, with groups 4 through 6 representing the most advanced. Comparison of the biopsy interpretations with the clinical groupings showed a good agreement between the clinical and pathologic data (table 4).

TABLE 4.—*Clinical Hypertensive Groups Compared with Kidney Biopsy Findings*

	Cases in preoperative hypertensive group					
	1	2	3	4	5	6
Kidney biopsy						
18 negative	4	1	12	1	0	0
Arteriolar sclerosis						
100 grade I	21	19	45	12	1	2
100 grade II	16	12	42	23	6	1
29 grade III	0	3	15	5	2	4
18 grade III and vascular necrosis	0	4	8	6	0	0
265 Total	41	39	122	47	9	7

Selective factors naturally were involved in the choice of patients for sympathectomy, but it is notable that of 41 cases in the clinical group 1, 25 had negative arterioles or arteriolar sclerosis grade I in kidney biopsies (61 per cent), while of 16 cases in groups 5 and 6, 13 (81 per cent) showed renal arteriolar sclerosis grades II and III.

Discussion

From the clinical viewpoint, the value of kidney biopsy at the time of sympathectomy was not great, except that when arteriolar sclerosis grade III was present, a significantly lower percentage of survival was found 3 and 5 years postoperatively. In this subgroup, with the most severe and generalized renal vascular alterations, the pathologic grading pointed more accurately to a less favorable outcome than the clinical hypertensive grouping. Because patients with arteriolar nephrosclerosis grade III were older, the most essential factor responsible for the increased mortality appeared to be the irreversible generalized damage to their vascular systems.

All other groups with varying degrees of renal arteriolar sclerosis had practically the same rather favorable postoperative survival rates after sympathectomy. This is interpreted to mean that, short of the most generalized and extreme arteriolar sclerosis, some relaxation of renal vessels and an interruption of the natural tendency to progression of hypertensive cardiovascular disease was achieved.[13] This benefit from sympathectomy in essential hypertension has been independently reported by White.[14]

Kidney function, judged by phenolsulfonphthalein excretion, decreased postoperatively in only 13 per cent of the entire group, except for those with diffuse vascular necrosis. Sympathectomy perhaps benefited renal vessels relatively more than coronary or cerebral arteries. Diffuse fibrinoid necrosis of arterioles is often regarded as the morphologic indication of a clinically malignant hypertension, but this view is based usually upon retrospective investigations of autopsied cases. The present biopsy study emphasizes that diffuse fibrinoid arteriolar necrosis is found in the absence of

retinal papilledema,[7, 8, 15] at diastolic blood pressure levels below 150 mm. Hg[8, 9] and without the renal insufficiency[16] thought to be a requisite of malignant hypertension.

Arteriolar sclerosis as an effect of hypertension upon the renal vasculature was again supported by the pathologic findings; consequently abnormal arteriolar spasm was considered to precede any recognizable structural alterations.[2, 4]

Pathologic analysis suggests that fibrinoid necrosis reflects acceleration of the arteriosclerotic process, and that when interrupted by sympathectomy the process need not continue to a lethal conclusion. It is notable, however, that with fibrinoid arteriolar necrosis, a progressive postoperative decline in renal function occurred in 50 per cent of the cases analyzed, so that local destructive renal lesions often are to be expected accompanying vascular necrosis.

Arteriolar sclerosis with essential hypertension as judged by this and other studies was focal and irregular in its involvement of the renal arterioles, except in the most advanced stage. A similar irregular alteration of the arterial blood vessels elsewhere in the body may explain the lack of correlation between appearances of the renal and retinal arterioles. The status of the eyegrounds and renal vessels reflected in part the general alterations of the vascular system due to hypertension, and these single diagnostic facets were of most value when combined with all other available clinical and laboratory data to provide a composite evaluation of the patient. In this selected group treated by sympathectomy, the kidney biopsy did not usually prove of greater value than other methods of evaluating the severity and probable course of essential hypertension.

Summary

Renal biopsies from 1,251 cases of essential hypertension, obtained at sympathectomy, have been analyzed pathologically. Severe arteriolar sclerosis was found in 5.0 per cent, arteriolar necrosis in 2.0 per cent, and pyelonephritis in 13.4 per cent of cases. Moderate local variations in the arteriolar alterations were found in single biopsies and in about 40 per cent of bilateral specimens.

Clinicopathologic correlations in 305 patients showed a general correspondence between the degree of renal arteriolar sclerosis and the clinical evaluation, postoperative blood pressure response, and renal function judged by phenolsulfonphthalein excretion tests. Severe arteriolar sclerosis was associated with more advanced age and a higher mortality.

Diffuse fibrinoid arteriolar necrosis was not correlated uniformly either with papilledema or other clinical criteria of malignant hypertension, and was not indicative of a uniformly grave prognosis. The kidney biopsy is considered as ancillary to the other methods used in the clinicopathologic evaluation of the hypertensive state.

Summario in Interlingua

Biopsias renal obtenite al sympathectomia ab 1.251 casos de hypertension essential esseva analysate pathologicamente. Sever sclerosis arteriolar esseva trovate in 5,0 pro cento, necrosis arteriolar in 2,0 pro cento, e pyelonephritis in 13,4 pro cento. Moderate variationes local in le alterationes arteriolar esseva trovate in biopsias unic e in circa 40 pro cento del specimens bilateral.

Correlationes clinico-pathologic in 305 patientes monstrava un correspondentia general inter le grado de sclerosis reno-arteriolar e le evalutation clinic, le responsa de pression sanguinee postoperatori, e le function renal secundo tests del excretion de phenolsulfonphthaleina. Sever grados de sclerosis arteriolar esseva associate con etates major e un augmento del mortalitate.

Diffuse necrosis arteriolar fibrinoide non esseva uniformemente correlationate con papilledema o con altere criterios clinic de hypertension maligne. Illo non esseva un indication uniforme de prognosis disfavorabile. Le biopsia renal es considerate como ancillari a altere methodos usate in le evalutation clinico-pathologic del stato de hypertension.

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Southey's Tubes

By ROBERT W. BUCK, M.D.

Southey's tubes. These are described by Reginald S. Southey (1835–1899) in the report of a case of "Chronic Parenchymatous Nephritis of Right Kidney. Left Kidney Small and Atrophied. Old Scrofulous Pyelitis" which was read before the Clinical Society of London, April 27, 1877 and which appears in the Transactions of the Clinical Society 10: 152–157, London, 1877.

"I determined to endeavour to relieve her dropsy by mechanical means, and to this end employed an apparatus which is, I believe, novel in England. I had a small trocar made, with tiny well-fitting canulas, but little larger than the ordinary subcutaneous injection needles; these canulas, instead of terminating with a protecting rim, end with a little bulbous extremity.

"They are inserted into the subcutaneous cellular tissue with great facility, and with no more pain than the ordinary needle-prick produces; the canula, inserted parallel to the surface, is left stuck in the skin; and a long, fine capillary india-rubber tubing is now drawn over the protruding bulb and tied *in situ*. This tying in of the canula is not essential or even often necessary.

"The long ends of the capillary tubes are now carried outside the bed and into a pan beneath it, into which the serous dropsical fluid drips or drains away.

"One drainage canula was inserted into each leg, and through the two tubes about 2½ pints, or, in fact, 71 ounces, of dropsical effusion drained away each 24 hours, with considerable relief, of course, to the tension."

Use of Different Tissue Thromboplastins in the Control of Anticoagulant Therapy

By MARC VERSTRAETE, M.D., PATRICIA A. CLARK, AND IRVING S. WRIGHT, M.D.

As anticoagulant therapy has become more widespread and a greater knowledge has been accumulated regarding the mode of action of coumarin derivatives, problems arising from the use of different thromboplastin preparations have been subjected to greater scrutiny. This paper presents an evaluation of the dependability and significance of different types of tissue thromboplastin in the determination of effects of coumarin derivatives. The main difference between thromboplastin extracts seems to be that brain preparations have a factor VII-like activity. As the exact evaluation of factor VII activity appears to be of primary importance in patients treated with coumarin derivatives, a thromboplastin preparation that does not contain factor VII activity is recommended.

AS THE indications for anticoagulant therapy become more extended, some problems in the management of anticoagulant therapy with coumarin derivatives and their laboratory control become increasingly important.

Until recently very little was known about the mode of action of coumarin derivatives. It has been shown that the activity of factor VII and subsequently of prothrombin decreases during coumarin therapy. This diminution is usually directly related to the antithrombotic activity of coumarin derivatives. Douglas[1] has recently shown that the prothrombin level of the blood does not fall below 50 per cent of normal during adequate therapy with 3,3′-carboxymethylenebis (4 - hydroxycoumarin) ethyl ester (Tromexan). The prolongation of the prothrombin time by the 1-stage method is partly due to the deficiency of factor VII and the moderate depression of prothrombin is insufficient to decrease blood coagulability. Recent studies have also demonstrated that the activity of other clotting factors, such as plasma thromboplastin component (PTC, factor IX, Christmas factor)[2, 3] and factor X[4, 5] decreases during coumarin therapy. The influence of coumarin derivatives on the latter 2 factors is not detected by the 1-stage prothrombin determination because potent tissue thromboplastin by-passes the first phase of the clotting mechanism in which both components participate. If the diminished activity of PTC and factor X is partly responsible for the desired hypocoagulability of the blood, the 1-stage prothrombin time method gives an incomplete account of the coumarin-induced changes. The heparin tolerance test, as a complementary test to prothrombin determinations, has given important information for the evaluation of the action of anticoagulants.[6, 7] This technic, however, is too cumbersome to become a routine procedure.[8]

Other problems are the presumably changing sensitivity of a given patient to a coumarin derivative and the varying dosage requirements by different individuals. These changes are evaluated on the basis of prothrombin assays carried out in the same laboratory with identical reagents.

A further shortcoming in the control of anticoagulant therapy is the lack of uniformity of prothrombin times in different laboratories using various technics and possibly different thromboplastins. Even the prothrombin time values obtained in one laboratory using the same technic but different thromboplastin preparations show significant differences.[9-13]

This communication is a report of a comparative study of the mode of action and properties of different thromboplastins used in the 1-stage prothrombin time test.

METHODS

Collection of Plasma. Blood was drawn into a syringe and added to tubes containing 0.1 M sodium

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oxalate in the proportion of 9 parts blood to 1 part sodium oxalate. Tubes that appeared to be underfilled or overfilled were rejected. The oxalated blood was centrifuged at 1,700 r.p.m. for 10 minutes and the plasma was removed.

Collection of Serum. Five to 10 ml. of venous blood were placed in a centrifuge tube. The clotted blood was stored in a water bath at 37 C. for at least 4 hours before the serum was removed. The presence of free thrombin in the serum was evaluated by adding 0.1 ml. of serum to 0.1 ml. of fibrinogen at 37 C. (fibrinogen Warner-Chilcott 300 mg. per cent). The prothrombin content was assessed in the mixture of 0.1 ml. of serum and 0.1 ml. of barium sulfate-treated plasma by adding 0.2 ml. of thromboplastin-calcium chloride suspension and observing the clotting time. For these experiments the rabbit lung extract, Difco-Aplastin, was used. Fifty milligrams of dried lung extract were suspended in 2.5 ml. of 0.85 per cent sodium chloride and mixed with 2.5 ml. of 0.02 M calcium chloride.

Preparation of Thromboplastins. Eight different commercial thromboplastin extracts were selected for this study. They were prepared in accordance with the methods described by the manufacturers. There were 4 rabbit lung preparations (Difco-Aplastin, Geigy Thromboplastin, Roche Thromboplastin, Warner-Chilcott Thromboplastin), 2 rabbit brain preparations (Alban Permaplastin, Difco Bacto-thromboplastin), 1 mixture of horse brain and lung extracts (Schieffelin Soluplastin), and 1 mixture of equal parts of rabbit lung and brain extracts (Warner-Chilcott Simplastin).*

Barium Sulfate Adsorption. One milliliter of oxalated plasma or serum was incubated at 37 C. for 10 minutes and shaken with 50 mg. of barium sulfate (Mallinckrodt, analytic reagent) and incubated at 37 C. for 10 minutes. The barium sulfate was separated by centrifuging at 1,700 r.p.m. for 10 minutes and the supernatant plasma was removed with a pipette.

Imidazole Buffer. Buffer solution, pH 7.4, ionic strength 0.618, was prepared by mixing 2.5 parts of imidazole solution (13.6 Gm. per 100 ml. of distilled water), 1.86 parts of 0.1 N hydrochloric acid, and 5.64 parts of distilled water.

Oxalated Buffer consisted of 9 parts of buffer solution and 1 part of 0.1 M sodium oxalate. Ionic strength of this solution was 0.658.

One-stage Prothrombin Time (Link-Shapiro). For the prothrombin time of whole plasma, approximately 0.5 ml. of plasma was transferred into a 75 by 100-mm. test tube and placed in a constant temperature bath at 37 C.

From the thromboplastin-calcium chloride suspension, 0.2 ml. was transferred into 100 by 12-mm. test tubes with a 0.2-ml. pipette (micro blood sugar). This suspension was blown into the test tubes with care to empty the pipette completely after each transfer. These tubes were placed in the rack beside the plasma samples in the constant temperature bath. As soon as the contents of the tubes reached the bath temperature, the prothrombin time of the plasma was determined by transferring 0.1 ml. of the warmed plasma to a tube containing 0.2 ml. of the thromboplastin-calcium suspension. The plasma was blown quickly from the pipette and at the same time the stop watch was started. The tube was tapped sharply to mix the solution. A small stirrer made of no. 22 nichrome wire with a small loop on the end was then introduced. If any small droplets were present on the sides of the tube, they were removed by passing the stirrer over them, thus making certain that all of the constituents were at the bottom of the tube. Only 2 or 3 seconds elapsed from the time the plasma was added to the thromboplastin-calcium chloride suspension. The mixture was stirred so that the stirrer loop swept across the test tube from one side to the other twice per second.

Results

Different commercial thromboplastin preparations, tested on the same day by the same technician using the same method, gave values ranging from 12 to 20 seconds for normal undiluted plasma. These differences in activity were greater when plasma with a prolonged 1-stage prothrombin time was tested. In order to determine if a conversion factor could be used to compare the results with different thromboplastins, dilution studies were performed. A hyperbolic relationship was found between the clotting time and the reciprocal of dilutions of normal plasma with barium sulfate-treated plasma. However, when prothrombin times versus reciprocal of plasma concentration were plotted, different curves were obtained for the various thromboplastins, although the technic and diluent were the same (fig. 1*A*). Figure 1*B* illustrates the results obtained with different vials of the same thromboplastin preparation, D-A; almost parallel straight lines resulted. In view of the differences in the curves of figure 1*A*, the 1-stage prothrombin times obtained with different thromboplastins cannot be compared directly and a conversion factor can-

* These materials will henceforth be designated as follows: Alban Permaplastin, A-P; Difco Bacto-thromboplastin, D-T; Difco Aplastin, D-A; Geigy Thromboplastin, G-T; Roche Thromboplastin, R-T; Schieffelin Soluplastin, S-S; Warner-Chilcott Thromboplastin, W.C.-T; Warner-Chilcott Simplastin, W.C.-S.

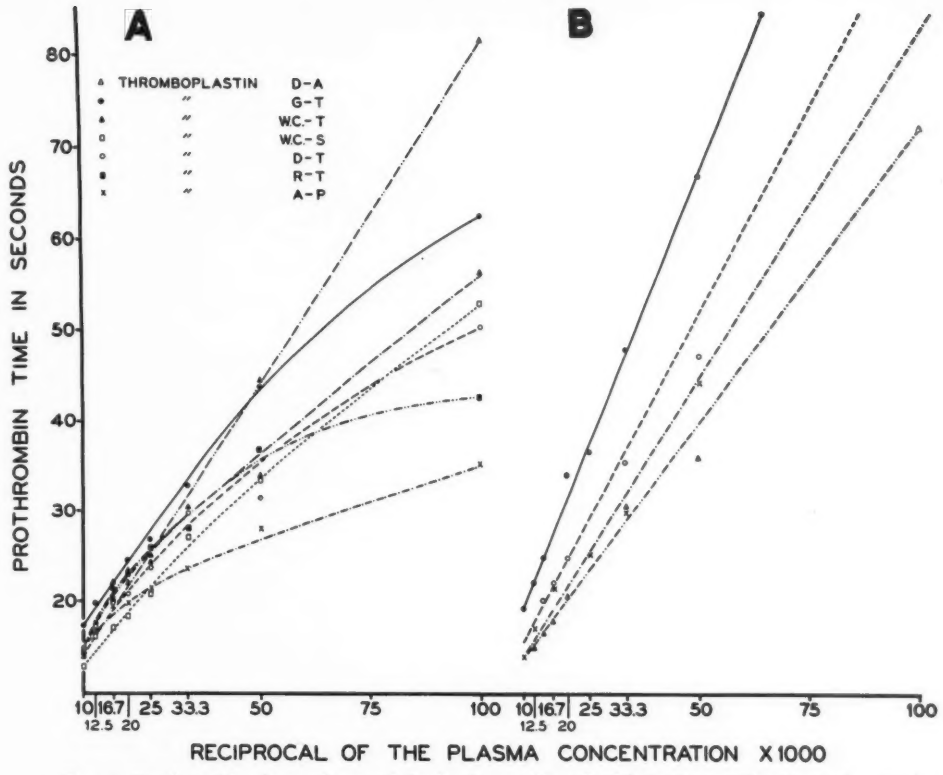

FIG. 1. Prothrombin times of normal fresh plasma diluted with barium sulfate-treated normal plasma performed (*A*) with various thromboplastins, (*B*) with the same thromboplastin (D-A) but with different vials having a slightly different activity.

not be used to correlate them. However, it is possible to make a calibration curve of one specific thromboplastin preparation.

Choice of the Diluent. When Quick introduced his valuable method of prothrombin determination in 1935,[14] 0.85 per cent sodium chloride was recommended as diluent. With plasma dilutions with 0.85 per cent sodium chloride, activity curves were plotted for the different thromboplastin preparations tested. When these curves were compared, they were found to differ considerably from each other (curves *D* in fig. 2*A–D*). There are, however, several objections to the use of 0.85 per cent sodium chloride, $\mu = 0.145$, as diluent. The determination of the clotting time is less accurate in the higher plasma dilutions because the fibrinogen concentration is low. Apart from the dilution of prothrombin, the concentration of 2 important accelerators (factor V and VII) of the thromboplastin-prothrombin-thrombin reaction is also decreased. One of them (factor V), is normally not affected by coumarin derivatives and is not supposed to be present in tissue thromboplastins. A decrease of the factor V content in the system leads, therefore, to a prolongation of the 1-stage prothrombin time that is not related to coumarin therapy. The final oxalate concentration also changes in the plasma diluted with 0.85 per cent sodium chloride. With imidazole buffer at pH 7.4, $\mu = 0.618$, (curve *A*, fig. 2*A–D*) the prothrombin times of serially diluted normal plasma were considerably shorter than in the previous experiments with 0.85 per cent sodium chloride. The presence of 0.01 M sodium oxalate in the imidazole buffer ($\mu = 0.658$) brought the dilution curves closer to those obtained with

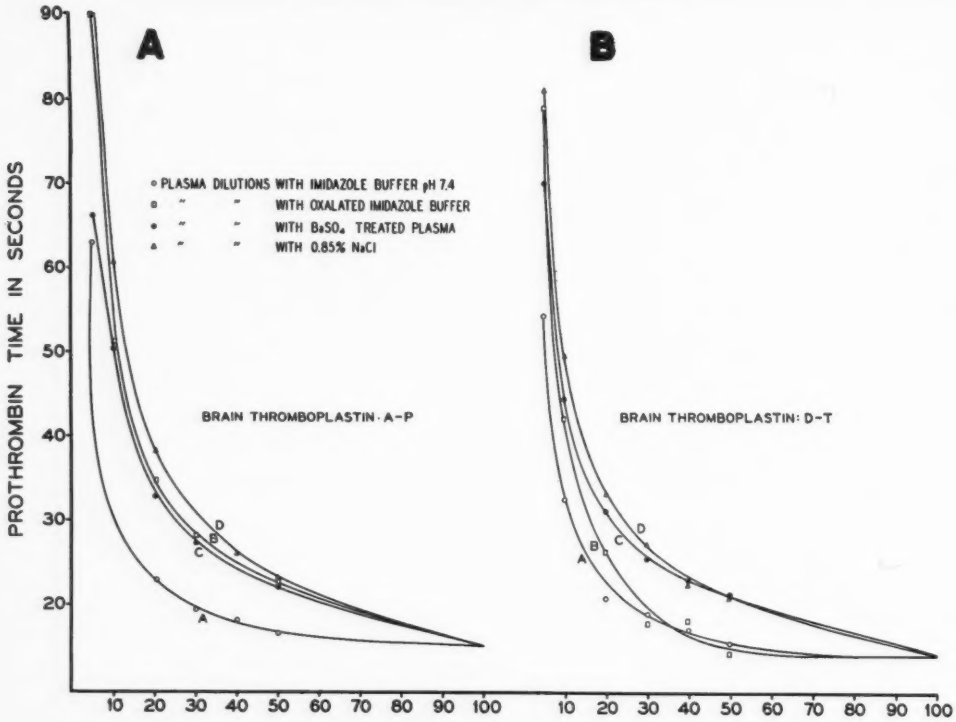

FIG. 2. Dilution curves of normal plasma with various diluents: (*A*) imidazole buffer pH 7.4, (*B*) imidazole buffer 7.4 containing 0.01 M sodium oxalate, (*C*) barium sulfate-treated normal plasma, (*D*) 0.85 per cent sodium chloride. The 1-stage prothrombin times were performed (*A*) with brain thromboplastin (A-P), (*B*) with brain thromboplastin (B-T), (*C*) with lung thromboplastin (D-A), (*D*) with lung thromboplastin (W.C.-T).

0.85 per cent sodium chloride as diluent (curves *B*, fig. 2*A–D*). From a consideration of the above-mentioned objections, a definite improvement in the technic was the use of barium sulfate-treated plasma as diluent (curves *C* of fig. 2*A–D*).[15] Adsorbed plasma provided factor V and fibrinogen but was devoid of factor VII, prothrombin, plasma thromboplastin component (PTC), partially free of plasma thromboplastin antecedent (PTA) and did not change the pH of the final mixture. The progressive decrease of PTC and PTA in the normal plasma dilutions did not influence the 1-stage prothrombin time because tissue thromboplastin by-passes their activity in the clotting mechanism.

In conclusion, for each thromboplastin tested, different dilution curves were obtained for the various diluents.

In an analysis of the data obtained with 4 different thromboplastins, a definite difference was noted between the plasma dilution curves for thromboplastin extracts derived from rabbit brain (A-P, D-T) and rabbit lung respectively (D-A, W.C.-T.). With the brain preparations there was only a moderate difference between the 1-stage prothrombin times in corresponding plasma concentration, with oxalated imidazole buffer or barium sulfate-treated normal plasma as diluent. Neither of the corresponding curves had a diverging slope in the lower plasma concentrations (curves *B* and *C* of fig. 2*A* and 2*B*). However, when the same experiments were repeated with thromboplastin prepared from rabbit lung, a marked difference between the results with oxalated imidazole buffer or barium sulfate-treated plasma was noted (curves *B* and *C* of fig. 2*C* and 2*D*). The di-

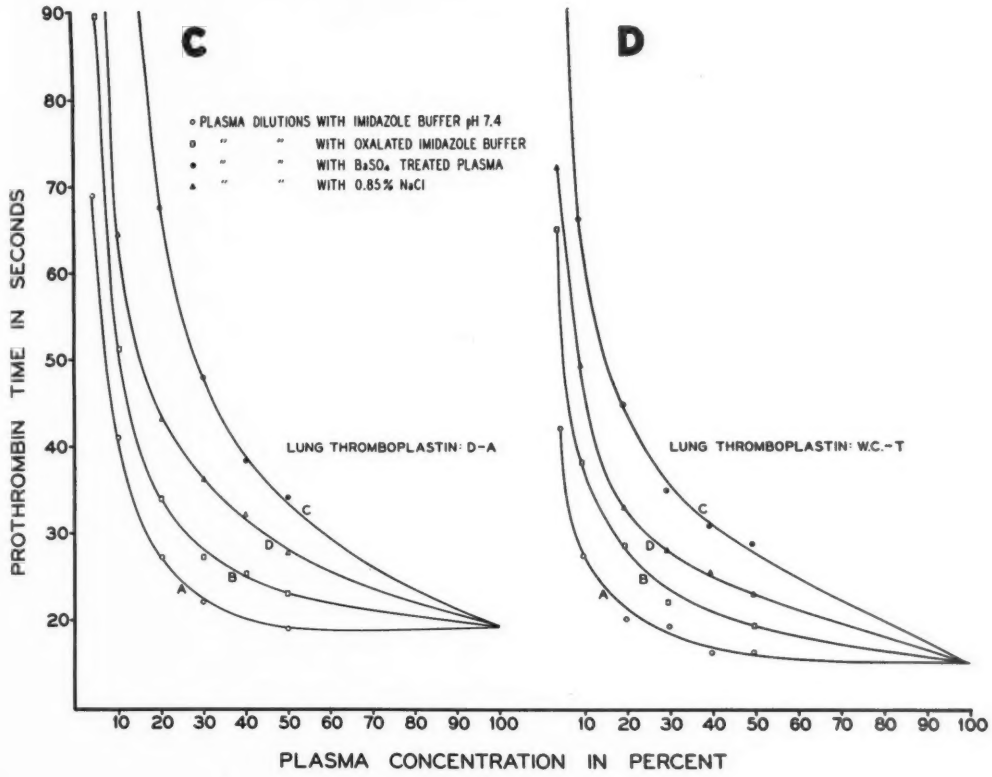

Fig. 2. *Continued.*

vergence between both curves became greater in the lower plasma concentrations.

The ideal diluent of the reference curve constructed for the guidance of coumarin therapy should be human plasma devoid of all the clotting factors that are influenced by the action of coumarin derivatives. It is difficult to define the content of this ideal diluent, since the exact influence of coumarin derivatives on blood clotting factors is not sufficiently understood. Therefore, the most suitable diluting agent is the plasma of a patient with a very prolonged 1-stage prothrombin time, induced by the action of a coumarin derivative (more than 3 minutes for undiluted plasma). Such plasma from human subjects is only rarely available. For this reason, animal blood was used for the following experiments. Daily doses of 10 mg. of 3 - (1′ - phenyl - propyl) - 4 - hydroxycoumarin (Marcumar) per Kg. body weight were administered orally to fasting rabbits, and blood was taken by cardiac puncture when the hypocoagulability was so marked that external bleeding occurred. The 1-stage prothrombin time of the pooled rabbit plasma was more than 3 minutes. The prothrombin time of normal rabbit plasma, tested with the same thromboplastin, ranged between 7 and 9 seconds (rabbit lung preparation D-A). Normal fresh rabbit plasma was diluted with the coumarin rabbit plasma and the 1-stage prothrombin time was determined with 2 brain thromboplastins (A-P and D-T), 2 lung thromboplastins (G-T and R-T), and 2 thromboplastins that are a mixture of lung and brain extracts (S-S and W.C.-S.). The same experiments were repeated on normal rabbit plasma diluted with barium sulfate-treated rabbit plasma. The results of these tests are shown in figure 3. From a consideration of a given

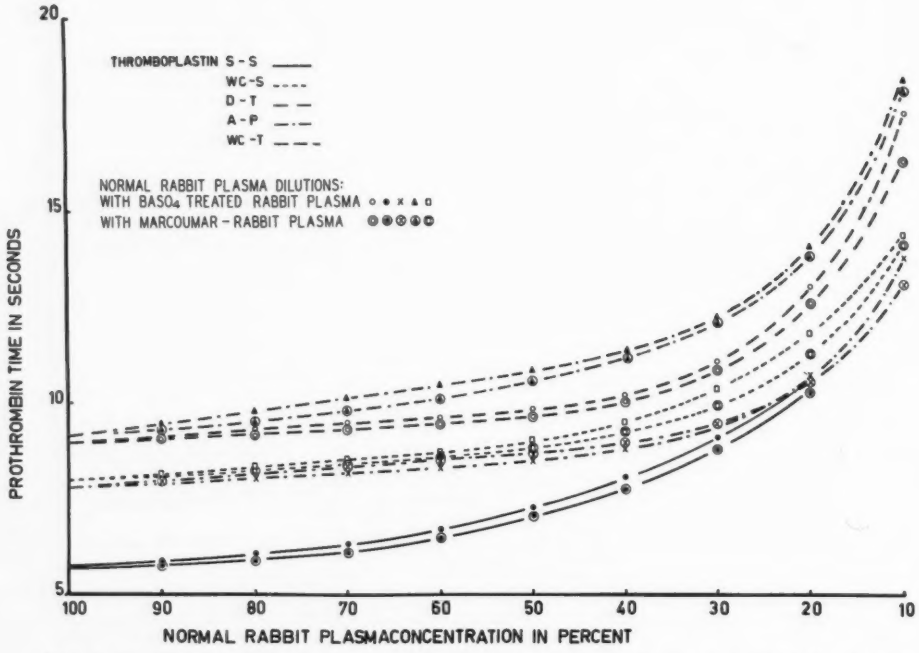

FIG. 3. Prothrombin times performed with various thromboplastins on normal rabbit plasma diluted with barium sulfate-treated rabbit plasma or plasma of a rabbit intoxicated with a coumarin derivative (3-(1′-phenyl-propyl)-4-hydroxycoumarin) (Marcumar).

thromboplastin, it is clear that the dilution curves with barium sulfate-treated rabbit plasma or coumarin rabbit plasma are practically superimposable. If human blood would behave in this respect as rabbit blood, it would indicate that for clinical purposes, barium sulfate-treated normal plasma may replace the "ideal" plasma with a very long 1-stage prothrombin time. This statement applies *only* to 1-stage prothrombin times performed in controlling therapy with coumarin derivatives.

Properties of Brain and Lung Thromboplastins. When the thromboplastins were diluted with calcium chloride and aliquots used with a fixed quantity of normal plasma in the 1-stage prothrombin time test, almost parallel curves were obtained in plotting clotting times against thromboplastin concentration (fig. 4). This result indicates that the basic difference between both groups of preparations is not directly related to the optimal concentration of materials that induce blood coagulation nor to the proportional concentration of substances that enhance or inhibit clotting.

The activity of both types of thromboplastin were further investigated in systems containing decreasing concentrations of prothrombin or factor VII. The clottable substrate consisted of 0.1 ml. of normal plasma diluted to various concentrations with the same plasma previously treated with barium sulfate. Added to this mixture were 0.1-ml. samples of either factor VII-free plasma containing prothrombin (citrated human plasma filtered through a 20 per cent asbestos filter pad) or prothrombin-free serum, containing factor VII. The factor VII-"free" plasma or prothrombin-"free" serum was diluted with oxalated imidazole buffer to complement the dilutions of the normal plasma (i.e., 0.1 ml. of 75 per cent normal plasma and 0.1 ml. of 25 per cent serum or factor VII-free plasma).

Filtration through 20 per cent asbestos pads renders human citrated plasma free of factor VII and removes only 10 to 20 per cent of the

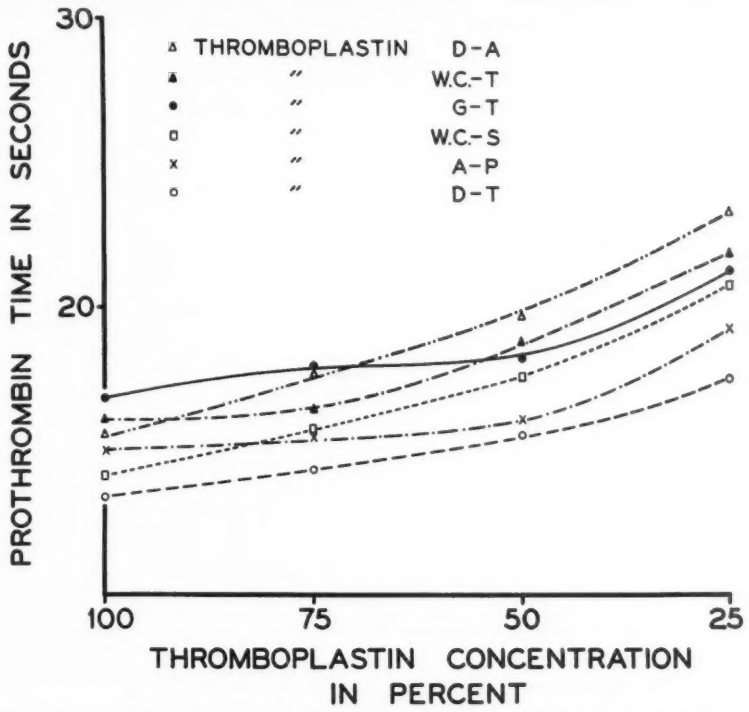

FIG. 4. Prothrombin times of normal fresh plasma performed with various thromboplastins diluted with 0.25 M calcium chloride.

original prothrombin concentration of the plasma. It is, however, important not to use the first 10-ml. filtrate, which is poor in prothrombin as well. Once the filter pad is saturated with prothrombin, only factor VII is adsorbed. Care should be taken not to overuse the filter beyond its adsorption capacity for factor VII. The presence of prothrombin in the filtrate is tested by adding in a constant volume increasing amounts of serum (source of factor VII) in order to obtain a 1-stage prothrombin time as close as possible to this of the unfiltered plasma. Usually 0.1 ml. of human serum, diluted 1 in 2 with imidazole buffer, will almost normalize the 1-stage prothrombin time of the filtered plasma (0.1 ml.) (1-stage prothrombin time before filtration, 14 seconds; of the filtrate, more than 3 minutes; of the filtrate-serum mixture, 16 seconds). If a normal prothrombin time can be obtained on the mixture of filtrated plasma and diluted serum, it can be concluded that the filtration did not remove substantial amounts of prothrombin.

The serum samples were free of active thrombin and the traces of remaining prothrombin were too small to interfere significantly in the experiments. The influence of salts, the pH, and the protein concentration on the 1-stage prothrombin time test and fibrinogen conversion has been stressed recently.[16, 17] The specimens were, therefore, diluted with oxalated buffer in order to keep the oxalate content and pH in the final mixture constant.

The thromboplastins were diluted with 0.25 M calcium chloride to the same extent as the normal plasma diluted with barium sulfate-treated plasma. The results of these experiments are shown in figures 5*A* and 5*B*. The points plotted represent the mean of 3 experiments performed in duplicate on 3 different days (tables 1 and 2).

When the factor VII content in the system was constant and the prothrombin level the only variable (fig. 5*A*), all the thromboplastin preparations tested appeared to have a similar activity. However, the results of the 1-stage

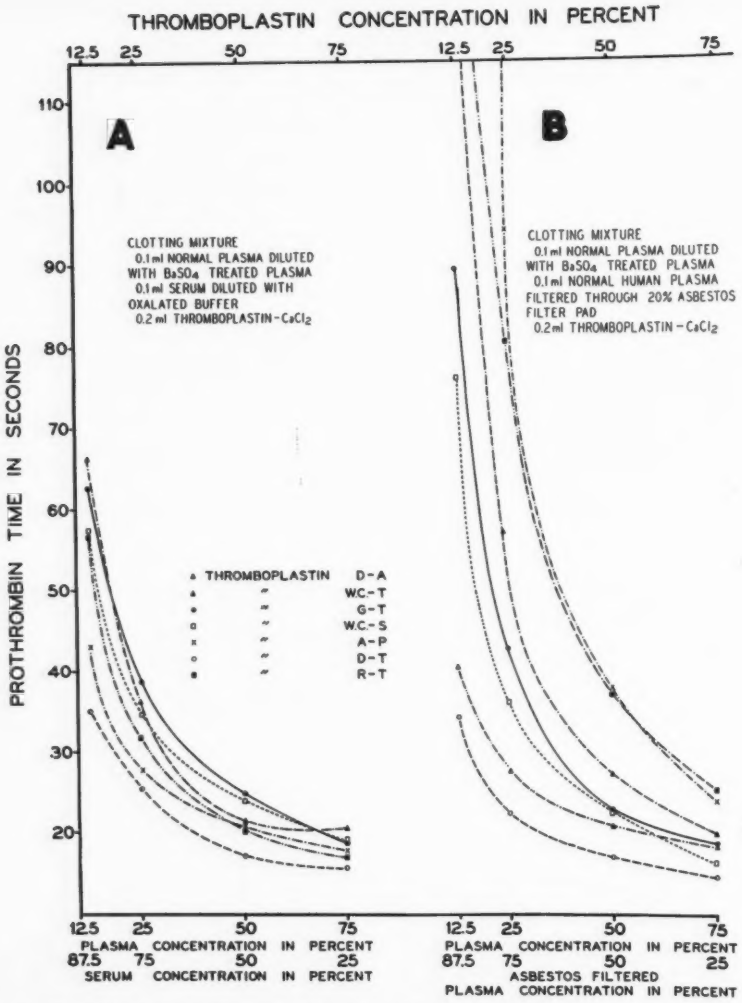

FIG. 5. Prothrombin times performed with various brands of thromboplastin on a clottable system containing (*A*) a fixed amount of factor VII and a decreasing prothrombin level (table 1), (*B*) a fixed amount of prothrombin and a decreasing factor VII level (table 2). The different thromboplastins were diluted with 0.25 M calcium chloride. Normal plasma was diluted with barium sulfate-treated plasma, and serum with imidazole buffer at pH 7.4 containing 0.01 M sodium oxalate. The points plotted represent the mean of 3 experiments performed in duplicate on 3 different days.

prothrombin time test were different when the clotting system had a fixed activity of prothrombin, but a varying content of factor VII (fig. 5*B*). The curves obtained with the various thromboplastins were now distributed over a large area and a significant difference between brain and lung preparations was apparent. The curves of prothrombin times measured with the brain extracts A-P and D-B were considerably flatter than those of lung preparations D-A, R-T, G-T, and W.C.-T. The prothrombin time curves for the thromboplastins consisting of mixture of both animal lung and brain extracts (S-S, W.C.-S) had an intermediate position.

In subsequent experiments, a fixed amount (0.1 ml.) of different buffer dilutions of normal

TABLE 1. *One-Stage Prothrombin Times in Seconds (Link-Shapiro Modification) C.T. Clotting Times of Three Experiments (Data for Fig. 5A)*

Concentration of prothrombin..	75%		50%		25%		12.5%	
Thromboplastin	C.T.	M	C.T.	M	C.T.	M	C.T.	M
Geigy (G-T)	19.0		31.5		51.5		74.5	
	17.5	18.7	19.2	24.6	23.8	38.2	45.9	62.6
	19.6		23.1		38.5		67.4	
Bacto brain (D-T)	14.4		17.5		30.1		42.8	
	14.0	15.5	13.9	17.1	22.3	25.4	29.6	35.0
	18.1		20.0		23.9		33.6	
Permaplastin (A-P)	18.3		22.2		29.6		53.0	
	14.0	17.7	14.3	20.6	20.7	27.7	30.3	43.0
	20.9		25.4		33.0		45.8	
Simplastin (W.C.-G.)	19.6		26.0		42.0		72.9	
	15.7	18.8	17.2	23.8	26.3	34.7	39.3	57.5
	21.3		28.3		35.8		60.4	
Aplastin (D-A)	14.3		16.3		29.0		48.8	
	—	16.9	—	20.4	—	31.7	—	56.7
	19.6		24.5		34.4		64.7	
Warner-Chilcott	27.9		31.4		38.3		84.7	
(W.C.-T.)	14.8	20.4	16.6	21.1	32.8	36.1	51.0	66.4
	18.7		25.5		37.4		63.6	

The thromboplastin suspensions were diluted with $CaCl_2$ M/40 to the same extent as the prothrombin concentration.

The factor VII content of the mixture is kept constant in these experiments.

TABLE 2.—*One-Stage Prothrombin Times in Seconds (Link-Shapiro Modification) C.T. Clotting Times of Three Experiments (Data for Fig. 5B)*

Concentration of factor VII.....	75%		50%		25%		12.5%	
Thromboplastin	C.T.	M	C.T.	M	C.T.	M	C.T.	M
Geigy (G-T)	17.5		18.9		33.2		55.8	
	18.6	18.6	24.8	22.7	46.7	42.6	109.0	89.5
	19.7		24.0		48.1		103.9	
Bacto brain (D-T)	12.8		13.5		17.0		25.0	
	16.2	14.5	20.6	16.9	27.3	22.2	40.1	34.2
	14.0		14.0		22.4		37.7	
Permaplastin (A-P)	15.6		16.3		20.2		31.0	
	21.9	18.2	25.3	20.8	35.8	27.4	57.0	40.2
	17.3		20.9		26.3		52.7	
Aplastin (D-A)	18.7		22.0		36.9		70.0	
	24.2	23.8	36.6	37.8	122.8	94.4	211.0	165.5
	28.6		55.0		123.5		—	
Warner-Chilcott (W.C.-T.)	15.3		16.6		27.1		48.0	
	22.6	19.9	29.7	27.0	89.5	57.1	+4′	
	22.0		34.9		53.7		—	
Simplastin W.C.-G.	15.0		15.7		23.0		38.2	
	16.1	16.4	27.2	22.6	47.7	36.0	111.0	76.0
Roche R-T	27.3		40.6		93.3		155.5	
	—	25.1	—	37.0	—	80.6	—	143.4
	22.9		33.4		68.0		131.3	

The thromboplastin suspensions were diluted with one-fortieth molar $CaCl_2$ to the same extent as the factor VII.

The prothrombin content of the mixture is kept constant in these experiments.

TABLE 3.—*One-Stage Prothrombin Times Performed on Mixtures of Equal Parts of Dicumarol Plasma and (A) Imidazole Buffer at pH 7.4, (B) Barium Sulfate-Treated Serum, (C) Normal Serum—The Serum was Diluted with Imidazole Buffer*

One ml. Dicumarol plasma plus	Thromboplastin used in testing pooled dicumarol plasma						
	W.C.-T.	D.-A.	R.-T.	G.-T.	W.C.-S.	A.-P.	D.-T.
A. 0.1 ml. buffer	28.8	32.2				21.8	30.6
B. 0.1 ml. $BaSO_4$, serum 1:5	31.8	37.2				22.4	20.4
C. 0.1 ml. serum diluted							
1:40	25.2	30.0				21.4	20.0
1:20	23.8	26.4				20.4	17.2
1:5	15.0	20.0				14.8	14.0
A. 0.1 ml. buffer	26.8	35.9	28.5	30.9	19.9	22.5	22.5
C. 0.1 ml. serum diluted							
1:50	18.8	19.6	19.7	21.4	16.0	16.5	16.1
1:40	17.9	18.2	20.0	19.9	15.4	15.9	16.1
1:20	17.2	17.2	18.1	19.0	15.0	15.7	15.3
1:10	17.4	16.5	17.8	17.4	14.8	15.9	16.1
1:5	19.1	16.0	18.1	17.3	17.4	16.0	16.3
1:2	22.6	19.8	18.5	19.6	21.0	18.8	20.7

TABLE 4.—*Activity of Lung Thromboplastin D-A and Brain Thromboplastin D-T on Normal Plasma and Dicumarol Plasma before and after Treatment with Different Concentrations of Barium Sulfate (2.5 mg., 5 mg., 10 mg., 25 mg., and 50 mg. per ml. Thromboplastin-Calcium Chloride Mixture), Incubation Time, 15 Minutes at 37 C.*

Thromboplastin	Not treated	Adsorbed with $BaSO_4$				
		2.5 mg. per ml.	5 mg.	10 mg.	25 mg.	50 mg.
D-A						
Normal plasma	19	21.2	24.2	23.2	23.8	30.6
Dicumarol plasma						
1	27.6	33.2	34.2	34.2	35.0	45.8
2	28.2	41.2	39.4	41.8	41.0	62.2
3	38.6	41.4	47.6	45.6	48.0	58.0
D-T						
Normal plasma	16.0	16.4	16.2	16.4	16.4	17.2
Dicumarol plasma						
1	22.0	21.0	21.2	22.0	19.6	20.0
2	25.4	25.2	24.0	25.8	25.0	25.6
3	26.2	25.0	25.8	26.8	25.0	23.8

TABLE 5.—*Activity of Different Thromboplastins on Dicumarol Plasma—Addition of Serum, Ether-treated Serum, or Barium Sulfate-Treated Serum to a Thromboplastin-Calcium Chloride Mixture*

	Mixture of 0.8 ml. thromboplastin-calcium chloride			
	A 0.2 ml. buffer	B 0.2 ml. serum	C 0.2 ml. ether-treated serum	D 0.2 ml. $BaSO_4$-treated serum
	0.2 ml.	0.2 ml.	0.2 ml.	0.2 ml.
W.C.-T	25.7	13.5	16.7	37
D-A	30.9	12.5	18.6	51.7
A-P	15.8	8.4	10.6	19.1
D-T	17.5	9.2	11.3	21.0

serum or barium sulfate-treated normal serum was added to 0.1 ml. of coumarin plasma. The prothrombin times of the mixtures containing untreated serum were shorter than those of the mixtures with adsorbed serum (table 3). To obtain the same reduction of prothrombin time of the Dicumarol plasma more serum was needed in the system if the tests were performed with lung rather than witb brain thromboplastins. From the results it is concluded that the difference in activity between both systems may be masked by addition of normal serum to coumarin plasma, but not by addition of barium sulfate-treated serum.

The opposite experiment was to treat the different thromboplastin-calcium chloride mixtures with barium sulfate (table 4). Even in a concentration of 50 mg. of barium sulfate per ml. of mixture, significant changes in the activity of brain thromboplastin were not noted. A lung preparation had a pronounced decrease in activity after similar treatment, even when very low concentrations of barium sulfate were used (2.5 mg./ml.).

The addition of 1 ml. of normal serum to 5 ml. of thromboplastin-calcium chloride mixture

enhanced the activity of brain and lung preparations. A moderately prolonged coumarin plasma reached even shorter values than the normal control time (table 5). If the serum (2 ml.) was shaken with ether (2 ml.) for 2 hours at room temperature before mixing with thromboplastin-calcium chloride, the 1-stage prothrombin time of the same coumarin plasma became equal to the control time (table 5*B*). However, if the serum was treated with barium sulfate before mixing with the thromboplastin-calcium chloride, the 1-stage prothrombin times became longer as compared with times obtained with regular thromboplastin (table 5*C*).

A further differentiation between lung and brain preparations could not be obtained by heating of the thromboplastin-calcium chloride mixtures to 60 C. or 90 C. for 10 minutes, because the activity decreased rapidly for both preparations.

Discussion

According to our clinical experience, the 1-stage plasma prothrombin time test is still the preferred method for the measurement of the action of coumarin derivatives. Although the exact influences of these compounds on the blood clotting factors are still obscure, the decrease of prothrombin and factor VII activity should be the guide for the administration of anticoagulants. Because coumarin derivatives produce a factor VII deficiency that may lead to bleeding without a striking depression of prothrombin, it is essential to evaluate factor VII in the plasma.

In order to make the 1-stage prothrombin time test reflect the factor VII and prothrombin content of the plasma, the thromboplastin used should be devoid of these factors. For example, Russell's viper venom combined with lipids had to be discarded because it possessed "convertin" activity.[15] When the action of rabbit brain and lung tissue thromboplastins was compared on plasmas of patients treated with coumarin derivatives, shorter times were obtained with brain preparations. In comparing the 2 groups of thromboplastins, it was found that both have a similar activity in a system with a fixed factor VII and decreasing prothrombin content. Brain preparations, however, gave significantly shorter times than lung thromboplastins if tested in a system with a fixed content of prothrombin but a decreased level of factor VII.

One possible interpretation of the observed difference between rabbit lung and brain thromboplastins is that brain preparations have a factor VII-like activity that does not seem to be present in lung preparations. Therefore, rabbit brain thromboplastins are more active than lung preparations in blood samples in which the concentration of factor VII is depressed. However, they have the same activity as lung preparations when the clotting system has a normal factor VII activity but low prothrombin activity.

The mode of action of rabbit brain thromboplastin is, therefore, similar to Russell's viper venom combined with lipids, which is considered to have a "convertin" activity (equivalent to the combination of antihemophilic globulin, PTC., factor VII and platelet lipid factor).[18, 19] The activity of the Russell's viper venom-lipid suspension is, however, considerably higher than that of brain extracts. The action of brain thromboplastin in the plasma prothrombin time is, therefore, partly independent of the factor VII content of the plasma tested. The practical clinical consequence is that when laboratories use brain thromboplastin, the clinicians have to give higher doses of coumarin derivatives in order to obtain the commonly accepted therapeutic prothrombin time than when the slower acting lung thromboplastin is used. A striking illustration of this is a large hospital where 2 laboratories are doing prothrombin times, using 2 different types of thromboplastin. When the blood is tested in one laboratory (using a brain thromboplastin), an average maintenance dose of 100 to 125 mg. of Dicumarol is required to maintain a prothrombin time of 25 to 35 seconds. However, when the tests are performed in the other laboratory, a daily dose of 25 to 50 mg. of Dicumarol is sufficient to maintain the prothrombin time in the same therapeutic range. The concept that a range expressed in absolute seconds can be accepted for all laboratories leads to absurd confusion. For example, a patient who appears

to be safely controlled on anticoagulant therapy according to the findings of one laboratory, might seem to be dangerously overdosed according to the results of another laboratory.

Most authors agree that the therapeutic range of the 1-stage prothrombin time is between 25 and 35 seconds or 1½ to 2½ the control time. Although most thromboplastins have a rather identical prothrombin time on fresh plasma, normal plasma has to be diluted much more to reach this therapeutic range, if a rabbit brain preparation rather than a lung preparation is used. To obtain a 1-stage prothrombin time of 30 seconds, normal plasma has to be diluted with barium sulfate-treated plasma to 34 per cent and 30 per cent if the prothrombin tests are performed with brain preparations (A-P and D-T respectively) and to 60 per cent and 45 per cent if a lung preparation is used (D-A and W.C.-T. respectively).

These observations indicate the hazard of referring to a prothrombin time without mentioning the control time, the type of diluent, and the thromboplastin used. In view of the marked difference in activity, it is almost impossible to determine a general therapeutic range for all thromboplastins commercially available. Previous attempts were based on the erroneous assumption that the thromboplastins are of fairly uniform activity.

Dilution curves of normal plasma with different diluents (0.85 per cent sodium chloride, imidazole buffer pH 7.4, oxalated buffer and barium sulfate-treated normal plasma) are quite different for each thromboplastin tested, although the different slopes are more similar for brain preparations than for lung preparations. When prothrombin times are reported in terms of concentrations of prothrombin, the diluent chosen to make the dilution graph should, therefore, be mentioned. As can be seen in figure 2*D*, curves *D* and *C*, a 20 per cent concentration (0.85 per cent sodium chloride dilution curve) corresponds to 35 per cent concentration (barium sulfate dilution curve) when W.C.-T. thromboplastin is used.

Summary

An analysis of the results of prothrombin time tests with different types of thromboplastin sheds some light on the problem why the administration of coumarin is difficult to standardize in different centers. Our present ideas on the subject, based on experimental data, may be summarized as follows.

Several factors of the clotting mechanism are influenced by coumarin derivatives. The action of some of these factors is by-passed in the 1-stage prothrombin time test. The decrease of the prothrombin and factor VII levels may be evaluated in the 1-stage prothrombin time determination (Quick test). The prolongation of the prothrombin times are, however, predominantly due to the decrease of factor VII activity, the prothrombin content remaining around 50 per cent of normal during an adequate anticoagulant therapy. It is unlikely that this degree of depression of prothrombin is of major significance in interfering with the coagulation mechanism in the protection against thromboembolism. It may, however, play a minor role, which has yet to be evaluated quantitatively. An exact evaluation of factor VII is, therefore, important for the guidance of anticoagulant therapy and the method of choice is the one that is most sensitive to changes in factor VII concentration. The 1-stage prothrombin time test with a rabbit lung thromboplastin seems the most suitable method because rabbit brain preparations exhibit a factor VII-like activity that is not present in rabbit lung preparations.

The 1-stage prothrombin time assay of normal plasma serially diluted with barium sulfate-treated plasma gives dilution curves that have a different slope for each thromboplastin tested, but are similar for different vials of one thromboplastin preparation.

When 0.85 per cent sodium chloride, imidazole buffer at pH 7.4, oxalated imidazole buffer, at pH 7.4, and barium sulfate-adsorbed normal plasma are used as diluents of normal plasma, different curves are obtained for each thromboplastin tested. With brain thromboplastin preparations, there is only a moderate difference between imidazole buffer curves and barium sulfate-treated plasma as diluent. However, when the same experiments were repeated with thromboplastin prepared from rabbit lung tissue, a marked difference between

he results obtained with the 2 diluents was observed.

The prothrombin times of clottable mixtures with a constant factor VII content and decreasing prothrombin activity obtained with lung and brain thromboplastins are spread over a small area. The same thromboplastins tested in a system with constant prothrombin activity but decreasing factor VII content give widespread prothrombin times. Brain preparations give short times; lung preparations give long times, and mixtures of lung and brain preparations take an intermediate position. The main difference between both thromboplastin extracts seems to be that brain preparations have a factor VII-like activity.

As the exact evaluation of the factor VII activity seems to be of primary importance in patients treated with coumarin derivatives, the use of a thromboplastin preparation devoid of factor VII activity is recommended.

Summario in Interlingua

Un analyse del resultatos de tests del tempore prothrombinic con differente typos de thromboplastina elucida a un certe grado le question proque le administration de coumarina es difficile a standardisar a differente centros. Nostre presente ideas in re iste thema—basate super datos experimental—pote esser summarisate sequentemente:

Plure factores del mechanismo coagulatori es influentiate per derivatos de coumarina. Le effecto de plures de iste factores es evitate in le uniphasic test del tempore prothrombinic. Le reduction de prothrombina e de factor VII pote esser evalutate in le uniphasic determination del tempore prothrombinic (test de Quick). Tamen, le prolongation del tempores prothrombinic es predominantemente le resultato de un reduction del activitate de factor VII, durante que le contento de prothrombina remane in le vicinitate de 50 pro cento del contento normal durante un adequate therapia anticoagulante. Il non es probabile que iste grado de depression de prothrombina es de signification major como obstruction del mechanismo coagulatori in le protection contra thromboembolismo. Del altere latere, il es possibile que illo ha un rolo de signification minor, que ha non ancora essite evalutate quantitativemente. Per consequente, un exacte evalutation de factor VII es importante como guida in le therapia anticoagulante, e le methodo de election es le methodo que es le plus sensibile a alterationes in le concentration de factor VII. Le uniphasic test del tempore prothrombinic con un thromboplastina de pulmon de conilio pare esser le methodo le plus appropriate, proque preparatos ab cerebro de conilio exhibi un activitate del typo factor VII que non es presente in preparatos ab pulmon de conilio.

Le essayo uniphasic del tempore de prothrombina in plasma normal con dilution serial per plasma tractate con sulfato de barium resulta in curvas de dilution que exhibi differente inclinos con omne le thromboplastinas testate sed que es simile pro differente tubos in que le mesme preparato thromboplastinic es usate.

Quando plasma normal es diluite con 0,85 pro cento de chloruro de natrium, tampon imidazol a pH 7,4, tampon imidazol oxalate a pH 7,4, o plasma normal adsorbite a sulfato de barium, differente curvas es obtenite pro omne le thromboplastinas testate. In le caso de preparatos de thromboplastina cerebral, il ha solmente moderate differentias inter le curvas correspondente al uso de tampon imidazol e de plasma tractate con sulfato de barium como diluentes. Tamen, quando le mesme experimentos esseva repetite con thromboplastina preparate ab tessuto pulmonar de conilios, un marcate differentia esseva observate inter le resultatos obtenite con le 2 diluentes.

Le tempores prothrombinic de mixturas coagulabile con constante contentos de factor VII e decrescente activitate prothrombinic obtenite con thromboplastinas pulmonar e cerebral es pauco variate. Le mesme thromboplastinas testate in un systema con constante activitate prothrombinic sed con un decrescente contento de factor VII resulta in multo divergente tempores prothrombinic. Preparatos cerebral produce breve tempores. Preparatos pulmonar produce longe tempores. Mixturas de preparatos pulmonar e cerebral produce tempores intermediari. Le principal differentia inter le duo extractos thromboplastinic pare esser que pre-

paratos cerebral ha un activitate resimilante factor VII.

Proque le evalutation exacte del activitate de factor VII pare esser de importantia primari in patientes tractate con derivatos de coumarina, le uso de preparatos thromboplastinic sin activitate de factor VII es recommendate.

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Let the medicine therefore be given in the doses, and at the intervals mentioned above:—let it be continued until it either acts on the kidneys, the stomach, the pulse, or the bowels; let it be stopped upon the first appearance of any one of these effects, and I will maintain that the patient will not suffer from its exhibition, nor the practitioner be disappointed in any reasonable expectation.—William Withering. *An Account of the Foxglove, and Some of Its Medical Uses.* Birmingham, 1785.

Serum Lipid Levels in Normal Persons

Findings of a Cooperative Study of Lipoproteins and Atherosclerosis

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THIS paper describes some of the findings of a cooperative research project on lipoproteins and atherosclerosis. The laboratories that participated in this study were Cleveland Clinic Foundation (Cleveland); Donner Laboratory, University of California (Donner); Department of Nutrition, Harvard School of Public Health (Harvard); and Department of Biophysics, University of Pittsburgh (Pittsburgh). A previous report[1] dealt with the relation of serum lipid levels in "normal" persons and the subsequent development of coronary artery disease. The history and organization of the study, as well as the various methods used and technical problems encountered, were described there.

The formal organization of the Cooperative Study was dissolved with the publication of that report but some of the original participants agreed to join as individuals in an additional analysis of the data collected in the Cooperative Study. This is given in the present report, which is concerned with lipid levels within the study population and their relation to race, age, sex, blood pressure, and weight. It deals only with persons who qualified as clinically normal for the purposes of this study. While the list of disqualifying characteristics given in the earlier report is comparatively long, the major exclusions were persons with evidence of coronary artery disease and persons with blood pressures in excess of either 170 mm. Hg systolic or 100 diastolic. The 2 lipoprotein fractions S_f 12–20 and S_f 20–100 and total serum cholesterol are considered.*

Since the Cooperative Study was designed to test the effectiveness of lipid levels as indicators of the likelihood of a coronary event in a clinically normal person, most of the data were collected from men 40 to 59 years old. The incidence of coronary disease is relatively high among men in this age span when compared with younger men or with women at the same age, while the prevalence of disqualifying clinical abnormalities is substantially less than at older ages.

Thirty-three different population sources were included in the study (table 1). Groups were chosen which appeared to be sufficiently stable so that a high proportion of their members could be followed one or more years. The groups were widely dispersed geographically. Two of them—the Los Angeles Civil Service Study and the Framingham Heart Study—were pre-existing cardiovascular study groups. Three source groups were prisoners at Federal penitentiaries (the "prisoners" referred to in the following discussion), and volunteers from the staffs of these penitentiaries were also included. The remainder of the sources can be described as employee or managerial groups. They included industrial workers, clerks, university employees and executives.

REPRODUCIBILITY

An obvious prerequisite for a joint study is the ability of the different laboratories to re-

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The report was drafted by an editorial subcommittee: Mr. Gordon, Dr. Hanig and Dr. Lewis. Statistical operations and analysis were directed by Mr. Gordon. Dr. J. Franklin Yeager acted as administrative officer of the group.

* Donner Laboratory has extended the range of lipoprotein fractions and modified the method of measurement for specimens from their sources. They have presented data for the 4 "standard" lipoprotein fractions and for indices based on these fractions.[2, 3] Those reports, however, did not present data for S_f 12–20 and S_f 20–100 as measured for this study.

TABLE 1.—*Summary Description of Groups Studied*

Laboratory and group	Location	Number of subjects*		Type of employment†	Method of selection
		Men	Women		
Cleveland					
White Motor Co.	Ohio	617	1	SSU	Volunteers
Chrysler Motor Co.	Mich.	1,172	243	SSU, clerical	Volunteers
Cleve. Grph. Bronze	Ohio	742	362	SSU, clerical	Volunteers
General Electric Co.	N. Y.	576	1	Executive	Annual examination
Nickel Plate Railroad	Ohio	102	—	Executive	Annual examination
Donner					
Framingham Heart Study	Mass.	1,555	1,829	Varied	Sample survey
City of Los Angeles	Calif.	861	166	SSU	Sample survey
Pan American Airways	Calif.	614	59	Executive, clerical	Annual examination
United Airlines	Calif.	215	—	Executive, clerical	Annual examination
Eastman Kodak Co.	N. Y.	711	158	Executive, clerical	Annual examination
Harvard					
Am. Mutual Ins. Co.	Mass.	33	32	Executive, clerical	Annual examination
Dr. Burwell	Mass.	17	—	Executive	Annual examination
Campbell Soup Co.	N. J.	34	1	Executive	Periodic examination
Dr. Chapman	Mass.	43	—	Executive	Annual examination
Lahey Clinic	Mass.	312	21	Executive	Annual examination
Met. Life Ins. Co.	N. Y.	658	331	Clerical	Annual examination
Mass. Inst. of Tech.	Mass.	236	—	Faculty	Annual examination
Rexall Drug Co.	scattered	103	1	Executive, sales	Annual examination
Standard Oil of N. J.	N. Y.	35	1	Executive	Volunteers
Swift and Co.	Ill.	72	—	Executive, professional	Volunteers
Oxford Diabetes Study	Mass.	81	83	Varied	Sample survey
Upjohn Co.	Mich.	9	3	Professional	Volunteers
Pittsburgh					
Hoffman-LaRoche	N. J.	530	87	Professional, clerical, SSU	Annual examination
Weirton Steel Co.	W. Va.	550	11	SSU	Annual examination
Federal Prisons:	Ga.	236	—	Staff and inmates	Volunteers
	Kan.	201	—	Staff and inmates	Volunteers
	Ind.	74	—	Staff and inmates	Volunteers
Westinghouse Elec. Co.	Pa.	144	12	SSU	Annual examination
Armco Steel Corp.	Pa.	82	2	SSU	Annual examination
Ford Engineering Co.	Mich.	75	—	Professional	Annual examination
All sources	—	10,690	3,404	—	—

* Includes all men and women who were normal at entry to the study.

† Type of employment for the largest groups studied at each source. Most industrial groups contributed some clerks, supervisors, and executives to the study. The designation "SSU" refers to skilled, semiskilled, or unskilled workers.

produce measurements. The steps taken to achieve reproducibility and the success of these efforts have been discussed in the earlier report. The findings of the main reproducibility studies are summarized in table 2. These indicate that over the period of these studies, the average values obtained for cholesterol in aliquots of the same blood were nearly the same for the Cleveland, Donner and Harvard laboratories, while the Pittsburgh measurements were 10 per cent lower throughout the range of levels studied, probably because of colorimeter differences. Ten per cent has been added to the Pittsburgh values for cholesterol and the compensated values have been used in this paper. While this procedure is not without risk, it is validated by the fact that the population means for the laboratories closely parallel the means found for specimens in the reproducibility studies. The average values obtained for S_f 12–20 on aliquots of the same blood were also reasonably consistent from laboratory to laboratory, except for a higher average at Donner, but unlike the cholesterol averages, the S_f 12–20

TABLE 2.—*Results of Between-Laboratory Reproducibility Studies in Relation to Population Values (Levels in mg. per 100 ml. Serum)*

	Between-laboratory reproducibility studies—1/52–6/53		Within-laboratory reproducibility —9/51–6/53		Population values	
	Mean	Technical error	Technical error	Relative technical error*	Mean	S.D.
Cholesterol						
Cleveland	183.7	3.2	7.6	.02	241.9	49.6
Donner	183.0	4.8	17.3	.14	241.2	47.0
Harvard	183.0	5.8	10.5	.05	242.4	45.0
Pittsburgh	169.7	6.3	5.0	.01	218.5†	46.4
S_f 12–20						
Cleveland	35.1	3.7	4.7	.05	33.6	21.1
Donner	40.3	4.1	4.7	.04	47.9	24.2
Harvard	35.9	4.5	5.1	.06	39.3	20.7
Pittsburgh	36.6	4.6	5.5	.05	45.0	24.3
S_f 20–100						
Cleveland	71.9	9.7	11.0	.03	83.6	64.9
Donner	75.9	8.6	12.3	.03	106.2	75.2
Harvard	64.2	8.0	9.6	.02	85.7	62.3
Pittsburgh	69.8	9.9	9.9	.02	101.7	78.3

Note: Population values are for men 40 to 59 normal on initial examination, and exclude Los Angeles and prisoner data.

* (Technical error)²/(population standard deviation)²

† Not adjusted.

mean population values by laboratory did not parallel the mean values obtained in the reproducibility studies. The measurement of S_f 20–100 varied more both within and among laboratories than was the case for cholesterol and S_f 12–20. The S_f 12–20 and S_f 20–100 values are therefore not adjusted.

The findings of the reproducibility studies are interesting in another respect. They show that the technical error,* while by no means negligible, and occasionally high, was still small enough that a cholesterol or lipoprotein level could be assigned to a single blood specimen with considerable confidence, as may be judged by the relative technical errors shown in table 2. The relative technical error—(technical error)²/(population standard deviation)²—indicates how well a technic allows one to distinguish 2 different blood specimens. This error is in general equivalent for the 2 lipoprotein fractions and cholesterol, and is very low on the average. Temporal fluctuations in lipid levels were not investigated as part of this study.[4]

* Technical error = $\sqrt{\Sigma d^2/2k}$, where k is the number of duplicates and d is the difference between duplicates.

RESULTS

Lipid Levels by Source

While table 3 indicates that the average level of S_f 12–20, S_f 20–100, and cholesterol of serum varied from source to source, the general similarity of lipid levels for the various sources is noteworthy. The great variety of geographic location, type of work, social class, and ethnic group might well have been expected to lead to much greater differences in lipid level. There also was no uniformity in the length of time since ingestion of food nor in the immediately preceding physical activity prior to the collection of blood samples.

Only 2 of the 33 groups differed significantly from the average: Los Angeles civil service employees and the penitentiary inmates. Los Angeles was notable for high average levels of cholesterol and S_f 12–20 and for a low level for S_f 20–100. The prisoners were distinguished by very low levels both for the 2 lipoprotein fractions and for cholesterol. No convincing explanation for either of these exceptions was discovered. Since the comparisons were originally made on the basis of means for each age and sex group, age and sex were already accounted for. The data—and especially those for Los Angeles—were examined for any artifacts of measurement that could account for the reported differences. None were found. Except for the fact that specimens were drawn from fasting subjects at Los Angeles, there is nothing to distinguish the group at Los Angeles from other groups in the study. The Los Angeles group was divided into 2 groups on the basis of kind of work—one essentially a laborer group and the other essentially a clerical group—but these were found to have similar lipid levels. The prisoner group, on the other hand, probably did a greater amount of physical work than most of the other subjects in the study. Their diet—on the limited data available—appears to be similar to that of an aver-

TABLE 3.—*Mean Lipid Values and Standard Deviations by Source, Men, 40 to 59*
(Levels in mg. per 100 ml. Serum)

Laboratory and source	Number of men*			Mean values			S. D.		
	S_f 12-20	S_f 20-100	Cholesterol	S_f 12-20	S_f 20-100	Cholesterol	S_f 12-20	S_f 20-100	Cholesterol
Cleveland	*1,557*	*1,544*	*683*	*33.6*	*83.6*	*241.9*	*21.1*	*64.9*	*49.6*
White Motor Co.	277	272	—	32.0	76.2	—	18.7	67.7	—
Chrysler Motor Co.	531	527	242	33.1	77.3	236.3	24.0	58.3	49.3
Cleve. Graphite Bronze	318	318	69	36.6	103.3	245.1	22.6	78.0	54.7
General Electric Co.	358	354	299	33.6	84.2	247.0	17.3	59.7	48.0
Nickel Plate Railroad	73	73	73	29.3	68.1	236.7	14.5	43.7	50.2
Donner†	*1,817*	*1,817*	*1,450*	*47.9*	*106.2*	*241.2*	*24.2*	*75.2*	*47.0*
Framingham Heart Study	899	899	761	47.0	113.3	238.9	21.8	84.5	45.0
City of Los Angeles	713	713	566	55.4	83.8	263.4	26.0	60.0	59.3
Pan American Airways	312	312	236	48.3	96.5	237.9	31.4	79.1	45.0
United Airlines	199	199	96	46.4	103.0	266.0	19.3	57.2	47.7
Eastman Kodak Co.	407	407	357	50.3	99.3	241.5	25.0	53.6	50.3
Harvard	*1,157*	*1,156*	*1,046*	*39.3*	*85.7*	*242.4*	*20.7*	*62.2*	*45.0*
Lahey Clinic	221	220	179	37.6	82.5	247.0	20.3	59.6	46.3
Metropolitan Life Ins. Co.	571	571	570	39.0	85.3	241.3	18.9	58.9	44.9
Mass. Inst. of Technology	98	98	98	39.9	77.5	244.9	19.1	60.2	49.3
Rexall Drug Co.	51	51	51	42.3	87.7	232.1	22.3	64.6	47.4
Swift and Co.	54	54	40	41.6	100.8	240.4	26.7	73.1	41.5
All others‡	162	162	108	40.9	90.8	243.7	24.9	72.6	39.3
Pittsburgh§	*840*	*836*	*837*	*45.0*	*101.7*	*240.4*	*24.3*	*78.3*	*46.4*
Hoffman-LaRoche	208	206	206	44.2	90.3	247.0	20.8	61.6	47.1
Weirton Steel Co.	408	408	407	46.3	103.5	242.0	24.8	88.3	45.9
U. S. Penitentiaries: Prisoners	326	325	326	36.5	96.5	215.8	18.6	57.7	39.9
U. S. Penitentiaries: Staff	172	172	172	42.2	108.6	230.8	25.2	71.2	44.6
All others‡	52	50	52	47.1	109.5	233.8	29.2	72.5	49.4

* Includes men without regard to follow-up who were normal at entry to the study.

† Data for Los Angeles excluded from total.

‡ Sources with less than 50 men are not shown separately but are included in the residual group for the laboratory.

§ Data for prisoners excluded from total.

age American, high in calories and in fats. Despite this, the prisoners weighed less on the average, height for height, than the other groups studied. Their blood pressures were decidedly lower, on the average, than those for other source groups in the study.

Lipid Levels by Race

Although race was frequently not reported, it is evident that the study groups were preponderantly white. The total counts were:

	Male	Female
White	6987	1328
Nonwhite	263	23
Not stated	3440	2053

It can be safely assumed that the "not stated" group included very few nonwhites and that almost all in the nonwhite group were Negro.

In light of the limitations of the data, it is difficult to characterize lipid levels for nonwhites on the basis of this study. The bulk of the nonwhite subjects were from Los Angeles and from the penitentiaries, both sources with unusual lipid levels. The S_f 20–100 levels were significantly lower in the nonwhite population at these sources than in the white, but there was, in general, no significant difference between the races for S_f 12–20 or cholesterol (table 4). Moreover, the source differences in S_f 12–20 and cholesterol levels were evident for both races. The S_f 12–20 and cholesterol levels for both the white population and the non-

TABLE 4.—*Mean Lipid Levels by Race, Men, 40 to 59, Selected Sources (Levels in mg. per 100 ml. Serum)*

	Number of men†			Mean values		
	S_f 12-20	S_f 20-100	Cholesterol	S_f 12-20	S_f 20-100	Cholesterol
Los Angeles						
White*	638	638	503	55.7	86.5	265.1
Nonwhite	75	75	63	53.0	61.1	249.1
Donner except Los Angeles	1817	1817	1450	47.9	106.2	241.2
Atlanta prisoners						
White*	84	83	84	39.0	102.7	216.3
Nonwhite	32	32	32	32.3	75.1	202.8
Leavenworth prisoners						
White*	140	140	140	35.5	101.2	220.0
Nonwhite	45	45	45	35.3	87.8	216.9
Pittsburgh except prisoners	840	836	837	45.0	101.7	240.4

* "White" includes "race not stated."

† Includes men without regard to follow-up who were normal at entry to the study.

white population at Los Angeles were higher than the average for other Donner sources. The S_f 12–20 and cholesterol levels for both the white and nonwhite prisoners at Leavenworth and at Atlanta were lower than the average for Pittsburgh, except prisoners. Furthermore, the lipid levels for nonwhites at the penitentiaries and at Los Angeles differed greatly. This argues that environmental differences associated with these 2 source groups (or some obscure artifacts of measurement peculiar to them) exert a greater effect on the level of S_f 12–20 and cholesterol than do racial differences, if such there are.

Distribution of Lipid Levels

Figures 1–3 and tables 5–7 give distributions for S_f 12–20, S_f 20–100, and cholesterol among men in the age group 40 to 59 years. This includes 60 per cent of the men studied. It is also the group of primary interest for epidemiologic and clinical studies in heart disease.

The lipid levels varied considerably from person to person, even among clinically normal populations. This is shown by the very large standard deviations in table 2. It is also shown by the range of values. Cholesterol values as low as 61 mg. per 100 ml. and as high as 509 were found in the 40 to 59 age group of men. S_f 12–20 levels ranged from 0 to 340 mg. per 100 ml., while S_f 20–100 levels ranged from 0 to 899 mg. per 100 ml.

Figures 1–3 indicate that the general distribution of lipid levels is similar in all the laboratories. The distributions are unimodal for all 3 lipid measures. More than one mode would suggest the presence of a distinct subgroup in the population that has unusual lipid levels, but our data do not support such a presumption. If such a subgroup, for example, a subgroup with a hereditary hyperlipemia, is included in the study population, it is too small to be distinguished in the general distribution of lipid measurements. Cholesterol has a relatively symmetrical distribution, though it is too skewed to the right to be represented by a normal probability curve. The skew is more marked for S_f 12–20 and even more evident for S_f 20–100. This means that the mode or value shown by the largest number of men is somewhat less than the average value for the group.

The cumulative frequency curves for S_f 12–20, S_f 20–100, and cholesterol (figs. 4–6) are especially useful. They show what percentage of the individuals for each group has measurements below any specified lipid level, and can, therefore, be used in evaluating a measure on any particular individual with reference to levels in the general population.

Age and Sex

The relation of serum cholesterol with age for men and for women is shown in figure 7 for all sources combined. The mean serum cholesterol level in men rises (but at a decreasing rate) from around 188 mg. per 100 ml. at age 18 to approximately 245 mg. per 100 ml. at age 55, after which the level declines. For women the pattern is somewhat different. At age 20, the cholesterol level in women is about the same as in men, but between age 20 and 30 the level in women rises only slightly. Thus, by 30 years of age the cholesterol level is approximately 20 mg. per 100 ml. lower in women than in men.

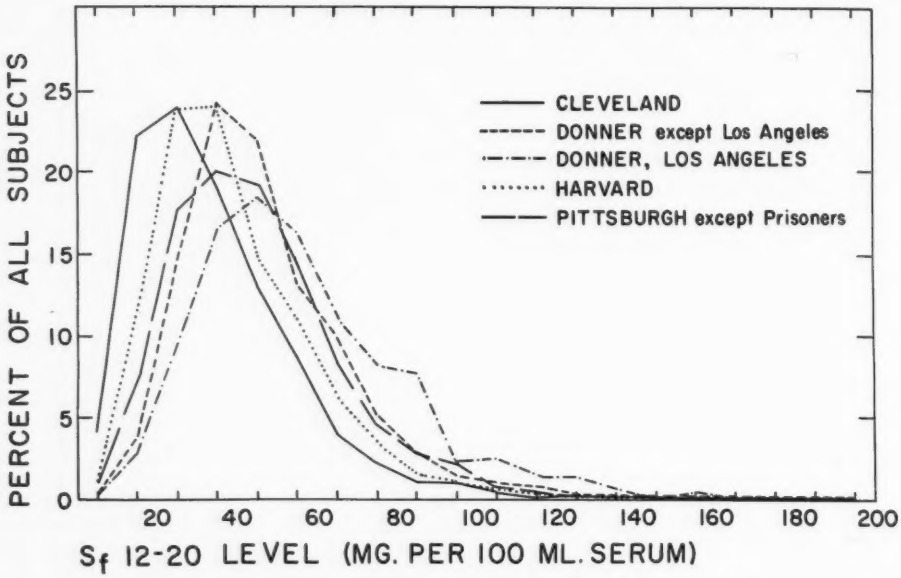

FIG. 1. Distribution of men 40 to 59 according to S_f 12–20 level.

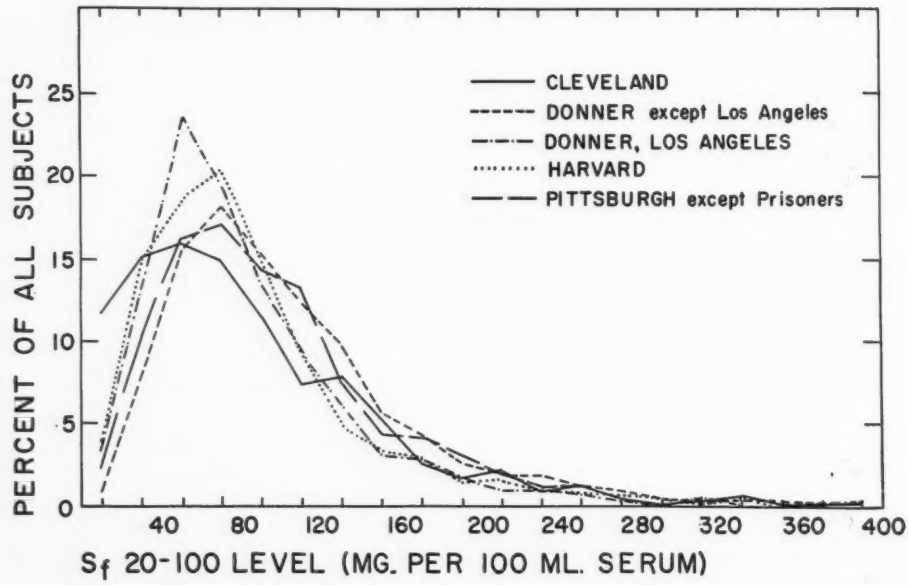

FIG. 2. Distribution of men 40 to 59 according to S_f 20–100 level.

After age 30 the cholesterol level in women rises at an increasing rate, so that above age 50 it is higher in women than in men. Whereas the level for men begins to decrease around age 55, the level for women, at least until 62, continues to rise.

This clear and simple picture of the relation of age and sex to lipid level can be given with

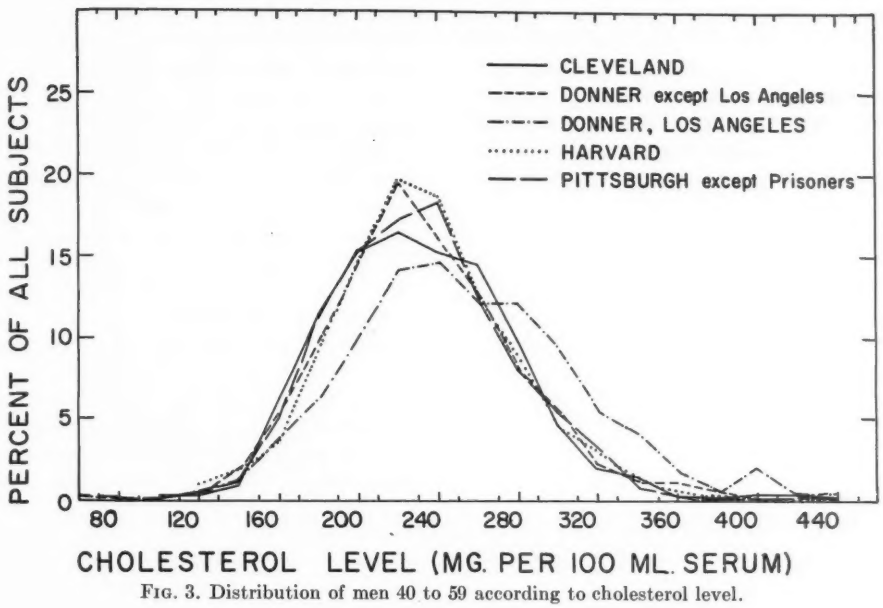

FIG. 3. Distribution of men 40 to 59 according to cholesterol level.

TABLE 5.—*S_f 12-20—Number of Subjects by Lipid Level, Men 40 to 59 (Levels in mg. per 100 ml. Serum)*

S_f 12-20 level	Cleveland	Donner		Harvard	Pittsburgh	
		Except LA	Los Angeles		Except prisoners	Prisoners
Total	1557	1817	713	1157	840	326
0-9	64	4	1	14	8	2
10-19	346	67	21	130	62	43
20-29	372	255	67	275	149	90
30-39	296	437	118	278	169	82
40-49	201	399	132	172	162	44
50-59	135	240	116	127	120	34
60-69	62	182	79	72	70	12
70-79	35	95	59	39	39	7
80-89	17	50	55	18	24	9
90-99	15	28	17	12	18	—
100-109	4	19	18	8	6	1
110-119	3	14	11	5	4	—
120-129	2	6	10	2	1	—
130-139	1	4	5	1	2	1
140-149	—	3	—	2	2	1
150-159	1	4	2	1	2	—
160-169	—	2	1	—	—	—
170-179	—	2	—	1	—	—
180-189	—	1	—	—	—	—
190-199	1	1	—	—	—	—
200+	2	4	1	—	2	—

TABLE 6.—*S_f 20-100—Number of Subjects by Lipid Level, Men, 40 to 59 (Levels in mg. per 100 ml. Serum)*

S_f 20-100 level	Cleveland	Donner		Harvard	Pittsburgh	
		Except LA	Los Angeles		Except prisoners	Prisoners
Total	1544	1817	712	1157	834	325
0-19	179	16	24	46	20	3
20-39	233	142	92	171	85	22
40-59	246	280	168	215	135	53
60-79	230	328	139	236	143	72
80-99	177	274	96	172	119	50
100-119	115	224	66	107	110	48
120-139	121	178	43	55	63	26
140-159	82	102	23	39	37	16
160-179	40	78	19	34	34	12
180-199	27	48	13	17	25	7
200-219	32	33	7	17	16	4
220-239	14	33	7	10	10	4
240-259	19	21	5	9	10	2
260-279	6	15	2	8	3	—
280-299	2	6	—	5	2	1
300-319	4	6	3	1	2	1
320-339	7	5	—	5	5	1
340-359	3	6	—	—	1	—
360-379	3	3	1	—	2	1
380-399	1	2	1	3	2	—
400+	3	17	3	7	10	2
No reading....	13	—	—	1	6	1

TABLE 7.—*Cholesterol—Number of Subjects by Lipid Level, Men 40 to 59 (Levels in mg. per 100 ml. Serum)*

Cholesterol level	Cleveland	Donner		Harvard	Pittsburgh	
		Except LA	Los Angeles		Except prisoners	Prisoners
Total	683	1450	564	1047	837	326
60–79	—	—	1	—	2	—
80–99	—	—	—	—	1	—
100–119	2	4	—	—	1	—
120–139	3	6	3	10	3	4
140–159	7	29	7	21	12	18
160–179	40	79	22	37	41	39
180–199	78	140	35	97	93	62
200–219	104	211	56	152	128	61
220–239	113	283	80	206	143	48
240–259	104	236	83	195	154	54
260–279	99	186	69	131	105	21
280–299	67	117	69	96	67	9
300–319	32	80	53	47	44	7
320–339	14	35	31	30	27	2
340–359	10	17	24	13	7	1
360–379	2	17	11	6	3	—
380–399	1	7	3	4	2	—
400–419	2	2	11	—	1	—
420–439	2	—	2	1	2	—
440–459	1	—	3	—	1	—
460+	2	1	1	1	—	—
No reading....	874	367	148	111	3	—

some confidence for serum cholesterol because the data from a large number of sources can be combined. Each point between ages 30 and 60 graphed for men represents the average of measurements on more than 100 men. No point for either curve is based on less than 10 cases. The curves were fitted by a least squares estimation of a third-degree polynomial, but because of the small numbers at the youngest and oldest ages the curve for men is carried only from age 18 to age 65 and the curve for women only from age 24 to age 62. The large number of measurements at each age, particularly for men, reduces the variability arising from differences between individuals and between groups. Even so, it may be seen from figure 7 that a large amount of fluctuation around the estimated trend remains, and it is conceivable that the basic biologic pattern is somewhat more complicated than this curve-fitting implies.

The difficulties that arise if the cholesterol data for each group are presented separately may be judged from table 8 and figure 8. Here the comparison is given by laboratory, omitting only data for Los Angeles and for the prisoner group. Averages are taken for 5-year

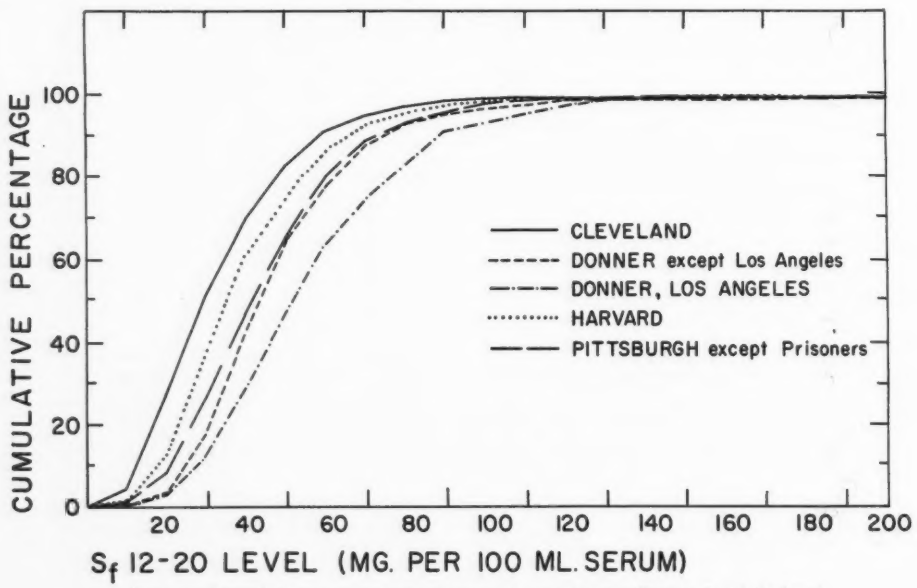

FIG. 4. Cumulative percentage of men 40 to 59 according to S_f 12-20 level.

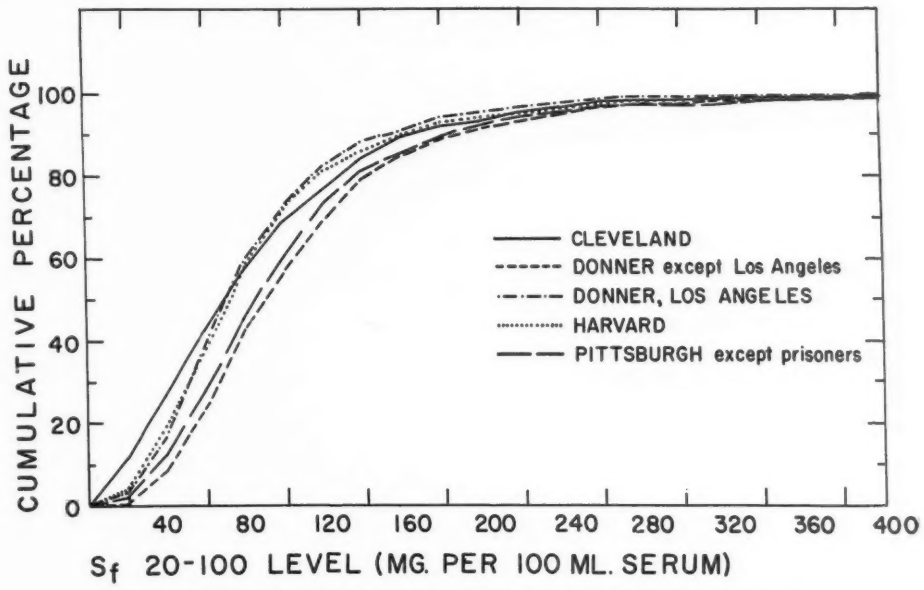

FIG. 5. Cumulative percentage of men 40 to 59 according to S_f 20–100 level.

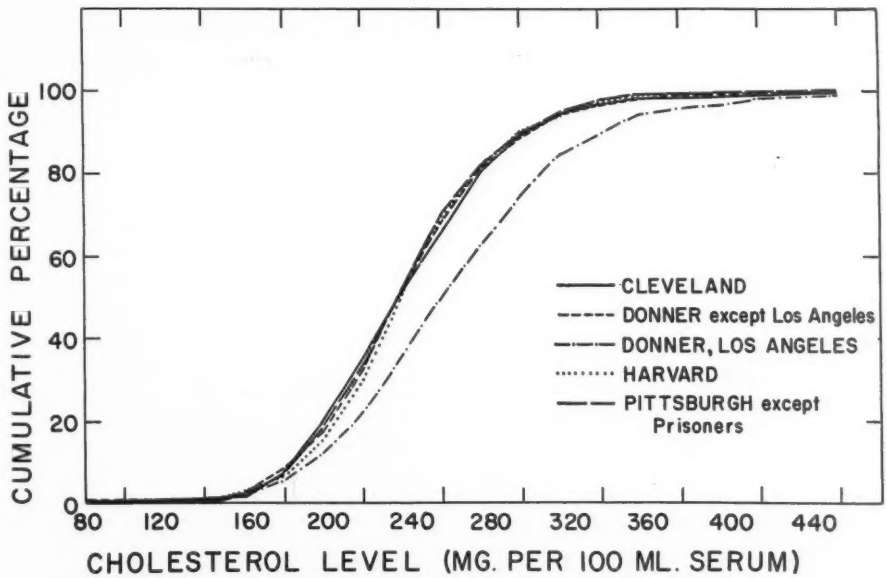

FIG. 6. Cumulative percentage of men 40 to 59 according to cholesterol level.

age groups and are omitted where measurements are available for less than 10 people. In this form of presentation the trends are somewhat confused and the data difficult to interpret.

It is reasonable to assume (although not certainly correct) that figure 7 represents the archetype for the relation of lipid level with age and sex for S_f 12–20 and S_f 20–100, as well as for cholesterol. While the data for S_f 12–20

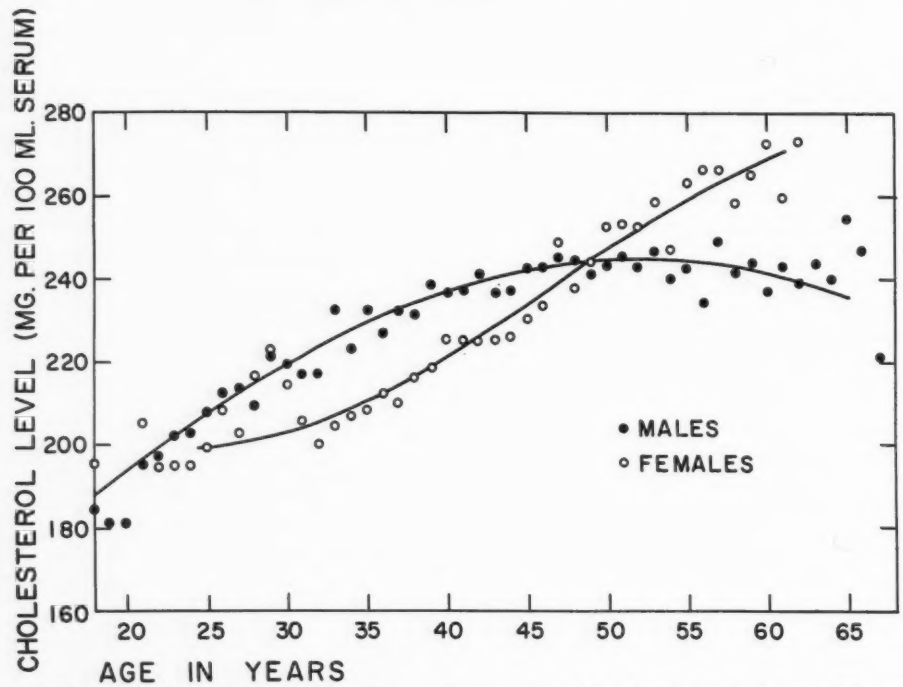

FIG. 7. Mean cholesterol level by age and sex: all sources except Los Angeles and prisoners. (Means based on less than 10 cases omitted.)

and S_f 20–100 presented in tables 9 and 10 and in figure 8 yield a somewhat confused picture —as might be expected from the comparable data for cholesterol—they are fairly consistent with cholesterol data. The only clear difference is in the comparison of S_f 20–100 level for men and women. The S_f 20–100 levels are consistently higher for men than women within the age span studied, though the difference is less with increasing age and may disappear among older people than those included in this study.

This raises the question to what extent can these data be extrapolated. The answer is, only to a limited extent. The curves shown in figure 7 cannot be safely extrapolated to the childhood years, nor can any definite indication of lipid levels for women older than age 65 be obtained from them. The study group supplied a scattering of data for older men, not included in this graph, which make it reasonable to assume that the cholesterol level for men continues to drop at least until age 80, although perhaps not so rapidly as the curve suggests.

If these data are to be used as a base reference for other studies, they must be used cautiously. The reproducibility studies showed that low technical error can be achieved only by considerable care. Furthermore, groups differ in lipid level, presumably because of both heredity and environment (e.g., diet, activity) and it is not at all clear that the population groups represented in the cooperative study provide a suitable base for judging what is "normal." For example, most of this population was employed and it is not evident that a 65-year-old man who is employed and who satisfies the rather restrictive clinical criteria of this study provides a suitable referrent for 65-year-old men in general.

The normal biologic dispersion of lipid measures is important when considering the application of these data to the evaluation of measurements made on an individual. In figure 9 the distributions of cholesterol levels in 2 age groups of well men are compared. While it is simple enough to distinguish the 2 groups, and, in fact, the mean levels differ markedly,

TABLE 8.—*Cholesterol*

Age group	Men						Women				
	Cleveland	Donner		Harvard	Pittsburgh		Cleveland	Donner		Harvard	Pitts-burgh
		Except LA	Los Angeles		Except prisoners	Prisoners		Except LA	Los Angeles		
Number of Subjects											
20–24	42	19	—	3	85	—	12	32	—	5	15
25–29	87	55	2	42	157	—	37	20	—	9	30
30–34	131	303	7	97	144	1	40	258	—	12	12
35–39	210	583	9	152	203	6	32	426	—	30	9
40–44	185	516	179	351	307	147	30	358	47	133	13
45–49	206	405	139	334	248	83	16	254	36	110	12
50–54	153	279	131	210	158	70	8	208	31	74	8
55–59	139	250	117	151	124	26	4	147	15	50	3
60–64	91	82	68	94	78	1	2	47	5	21	1
65–69	25	5	29	29	18	—	—	—	5	1	—
Mean values*											
20–24	200.6	209.5	—	—	195.4	—	213.4	188.8	—	—	198.5
25–29	212.3	213.0	—	211.6	214.6	—	218.6	205.3	—	—	205.4
30–34	227.8	219.1	—	221.4	225.5	—	229.5	200.7	—	209.1	224.6
35–39	237.5	229.8	—	229.0	236.2	—	226.7	212.4	—	206.6	—
40–44	242.9	237.8	258.9	237.3	235.4	215.5	227.5	228.0	248.3	218.2	229.0
45–49	240.8	242.6	257.9	244.7	245.3	215.6	228.0	241.4	226.5	231.8	253.1
50–54	244.6	246.9	269.6	244.1	239.3	216.7	—	255.6	259.6	242.9	—
55–59	239.3	239.5	269.7	246.6	244.4	215.5	—	267.9	293.6	256.6	—
60–64	242.3	237.1	263.0	243.2	239.5	—	—	274.4	—	246.8	—
65–69	248.4	—	258.1	244.7	245.1	—	—	—	—	—	—

Note: Mean values not calculated for groups with less than 10 subjects.
* Levels in mg. per 100 ml. serum.

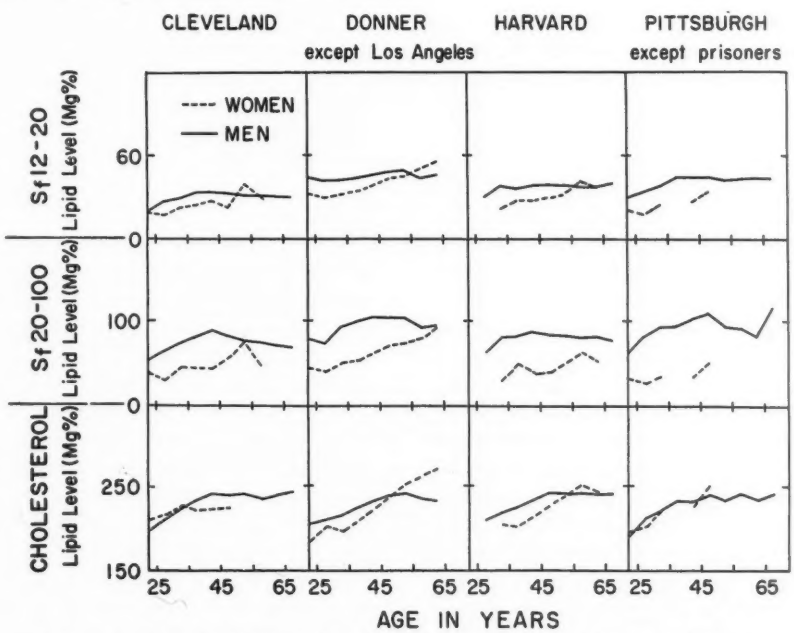

FIG. 8. S_f 12–20, S_f 20–100, and cholesterol: mean lipid level by age and sex.

TABLE 9.—*S_f 12–20*

Age group	Men						Women				
	Cleveland	Donner		Harvard	Pittsburgh		Cleveland	Donner		Harvard	Pitts-burgh
		Except LA	Los Angeles		Except prisoners	Prisoners		Except LA	Los Angeles		
Number of subjects											
20–24	121	26	—	3	85	—	59	36	—	6	15
25–29	317	58	2	45	158	—	99	24	—	9	30
30–34	436	354	8	107	146	1	138	298	2	14	12
35–39	534	722	12	169	203	6	124	490	—	31	9
40–44	539	647	214	393	309	147	82	424	56	138	13
45–49	425	514	173	366	249	83	49	305	43	115	12
50–54	321	356	173	233	158	70	24	240	34	76	8
55–59	272	300	153	165	124	26	12	161	18	50	3
60–64	165	106	90	102	78	1	5	61	7	22	1
65–69	44	6	32	31	18	—	1	—	5	1	—
Mean values*											
20–24	22.4	44.8	—	—	31.1	—	19.7	33.3	—	—	21.9
25–29	26.5	42.3	—	31.4	35.1	—	17.5	30.5	—	—	18.9
30–34	29.7	42.7	—	38.2	39.7	—	23.4	33.6	—	23.4	25.3
35–39	33.6	44.2	58.7	37.4	45.1	—	25.3	35.8	—	28.6	—
40–44	34.6	47.4	52.7	39.2	45.2	35.4	26.4	39.0	38.3	28.7	28.3
45–49	33.5	48.5	56.6	39.9	45.9	35.3	23.3	43.8	43.0	30.4	35.3
50–54	32.6	51.0	55.7	39.3	43.9	40.5	39.4	46.5	46.6	34.1	—
55–59	32.7	44.2	57.6	38.6	44.2	35.9	29.3	50.1	58.7	42.8	—
60–64	32.2	47.3	53.9	39.3	45.4	—	—	57.8	—	37.7	—
65–69	30.3	—	54.9	40.6	45.1	—	—	—	—	—	—

Note: Mean values not calculated for groups with less than 10 subjects.
* Levels in mg. per 100 ml. serum

the extent that these 2 distributions overlap is very striking. This is often a characteristic of biologic data but one that is frequently overlooked. It is especially important where a diagnostic criterion is being tested, for, to be of use, a diagnostic tool must allow a physician to decide whether an individual measurement belongs in the distribution for a "normal" population or an "abnormal" population, and these may overlap considerably.

The biologic dispersion of lipid measures is about the same for men and women. Figure 10 compares the distributions for men and women in the age group 40–59. These 2 distributions are almost indistinguishable. The means are the same because of an averaging effect across the specified age span. More important, however, is the near identity of the dispersion of values. Figures 11 and 12 present comparable data from one major source for S_f 12–20 and S_f 20–100. The distribution of S_f 12–20 values, like the distribution of cholesterol values in this age group, is nearly the same for both sexes. For S_f 20–100, on the other hand, there is a considerable sex differential in the curves, a differential comparable to that shown between men 25 to 29 and men 55 to 59, for cholesterol, in figure 9.

The question of whether the increase in serum cholesterol concentration with age is a normal physiologic process or whether it results from the development of some metabolic disorder that was not detected in the so-called "normal" individuals studied, cannot be answered from these data. In a group of people who were very carefully selected for normalcy, and studied by Page and co-workers,[5] no increase in cholesterol concentration with age was noted. Similarly, Milch and associates,[6] in a study of serum lipoproteins of airforce flying personnel, failed to find any consistent change with aging in cholesterol or phospholipid, but

TABLE 10.—S_f 20–100

Age group	Men						Women				
	Cleveland	Donner		Harvard	Pittsburgh		Cleveland	Donner		Harvard	Pitts-burgh
		Except LA	Los Angeles		Except prisoners	Prisoners		Except LA	Los Angeles		
Number of subjects											
20–24	121	26	—	3	85	—	58	36	—	6	15
25–29	315	58	2	45	157	—	95	24	—	9	30
30–34	430	354	8	107	145	1	137	298	2	14	11
35–39	530	722	12	169	201	6	122	490	—	31	9
40–44	536	647	214	393	307	147	80	424	56	138	13
45–49	422	514	173	366	248	83	48	305	43	114	12
50–54	318	356	173	232	157	70	24	240	34	76	8
55–59	268	300	153	165	124	25	12	161	18	50	3
60–64	163	106	90	102	78	1	5	61	7	22	1
65–69	43	6	32	31	18	—	1	—	5	1	—
Mean values*											
20–24	55.2	82.3	—	—	63.9	—	39.9	46.7	—	—	31.3
25–29	66.9	78.8	—	63.8	81.3	—	30.6	42.7	—	—	27.7
30–34	74.4	97.9	—	82.1	96.0	—	47.1	51.5	—	30.5	36.2
35–39	82.5	101.7	75.5	83.0	97.6	—	47.4	55.1	—	51.6	—
40–44	90.1	108.6	87.8	88.4	102.5	94.2	46.9	63.8	41.9	39.5	34.5
45–49	81.3	108.4	82.4	85.7	110.2	94.6	59.3	72.2	51.7	40.6	51.9
50–54	79.4	107.8	78.9	84.8	93.7	107.0	79.2	77.0	51.5	51.4	—
55–59	79.2	95.0	85.4	80.4	92.5	87.4	47.3	80.9	68.1	66.7	—
60–64	74.6	98.5	70.7	82.5	84.8	—	—	93.2	—	56.2	—
65–69	72.3	—	73.5	78.9	120.3	—	—	—	—	—	—

Note: Mean values not calculated for groups with less than 10 subjects.
* Levels in mg. per 100 ml. serum.

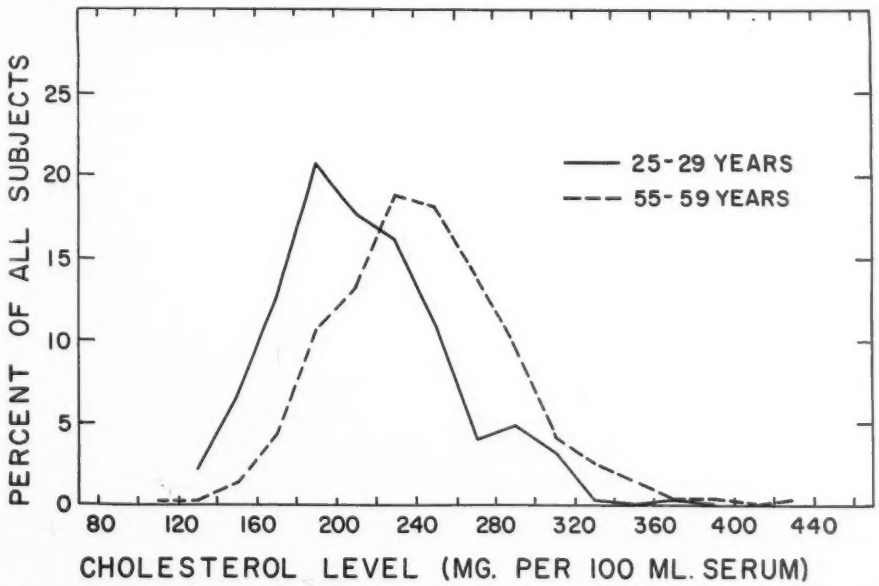

FIG. 9. Distribution of men 25 to 29 and 55 to 59 according to cholesterol level: all sources except Los Angeles and prisoners.

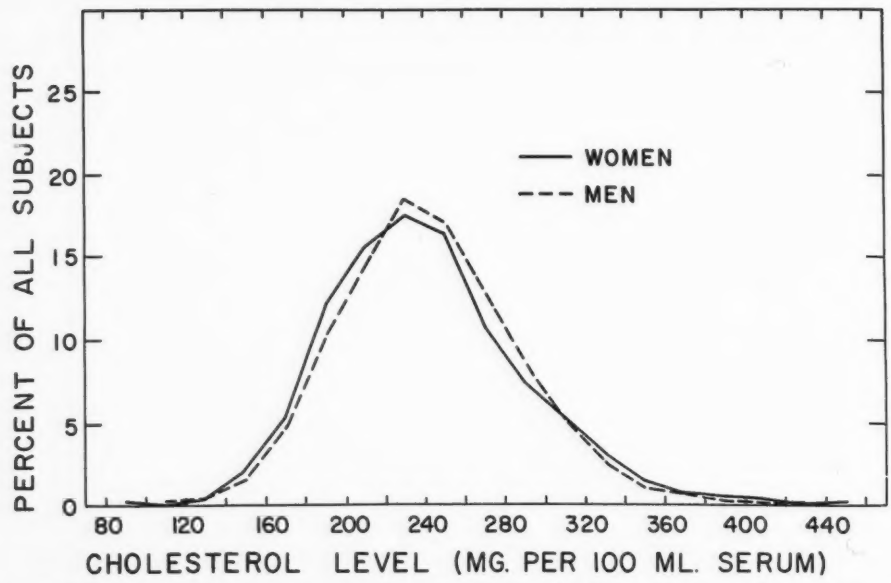

FIG. 10. Distribution of men and women 40 to 59 according to cholesterol level: all sources except Los Angeles and prisoners.

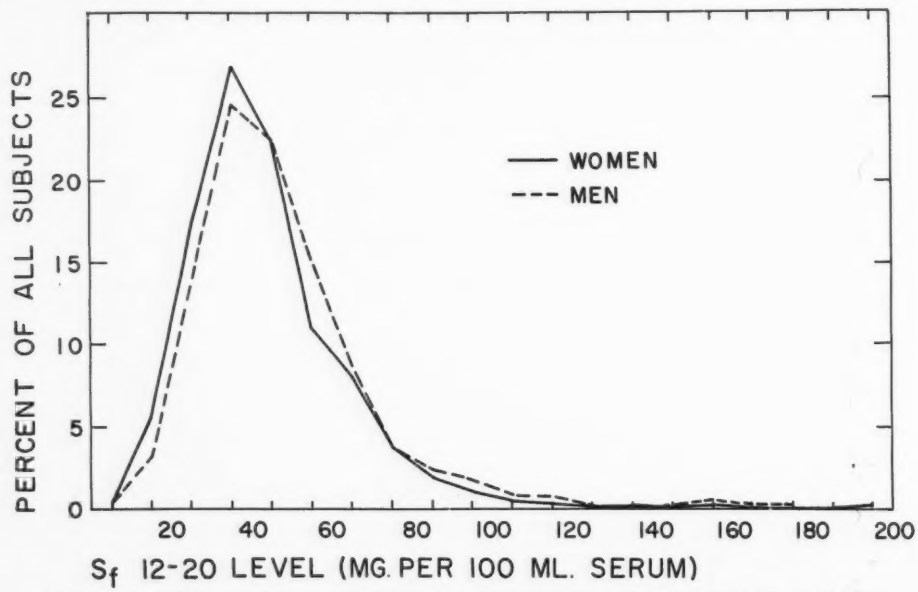

FIG. 11. Distribution of men and women 40 to 59 according to S_f 12–20 level: Framingham.

did find concentration increments for S_f 12–20 between 20 to 25, 25 to 35, and 40 to 45 age groups.

Keys et al.[7, 8] observed in populations (Minnesotans) subsisting on high-fat diets a trend toward a steady rise in cholesterol concentration with age. In contrast, a group of Neopolitan males, "who like most Italians

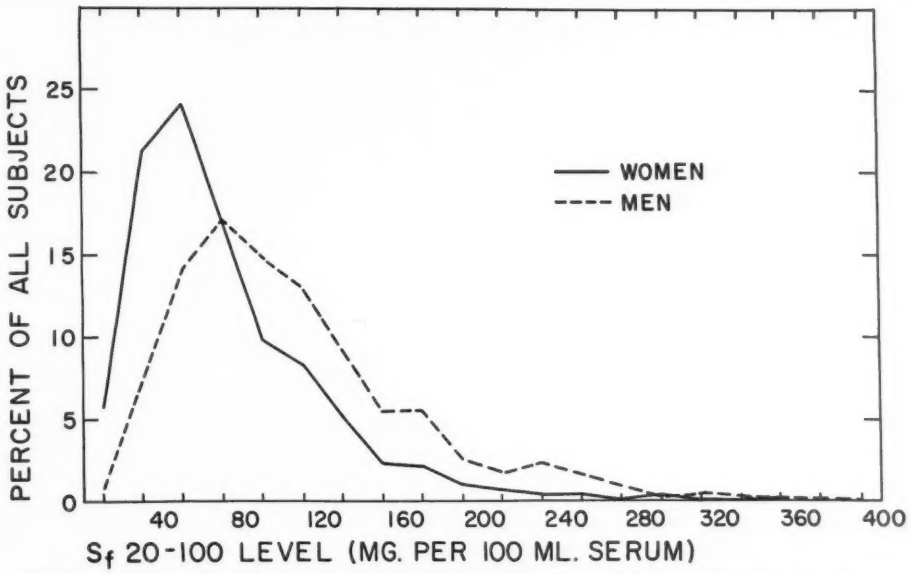

FIG. 12. Distribution of men and women 40 to 59 according to S_f 20–100 level: Framingham.

have a diet which is low in fat," showed an increased concentration of serum cholesterol to age 30, but not after that. Between ages 20 and 30 there was an increase of 3 mg. per year in both groups. The increase continued in the Minnesotans but not in the Neopolitans, so that by age 50 there was a mean difference of 30 mg. per 100 ml. Mann and co-workers[9, 10] concluded on the basis of studies among Nigerians and rural Guatemalans that there appeared to be "some environmental factors at work which prevent the rise of serum cholesterol levels with age which is characteristic of North Americans."

It should be pointed out that the data for age in all these studies, as well as in the present paper, derive from a population cross-section. They are not obtained by following individuals for a period of time to see how their lipid levels change. Serial changes have been reported for a small number of subjects (14 men and 8 women by Sperry and Webb[11] and 7 men and 9 women by Man and Peters).[12] The first study found no consistent change with age after an interval of 13 to 15 years in the serum cholesterol concentration. In some persons there was an increase, but it was not an obligatory circumstance of aging. The group studied by Man and Peters varied from 20 to 48 years of age at the time of initial observation and from 30 to 65 at the final. None of the subjects had known metabolic disorders and all were leading active lives. The cholesterol, fatty acid, and lipid phosphorus values revealed no consistent changes during these intervals. Although the values rose more frequently than they fell, this tendency was not so preponderant as to warrant the deduction that it is characteristic of aging.

The changes in the serum lipid pattern of females between the ages of 45 and 60 are probably influenced by a shifting hormonal balance associated with the premenopausal, menopausal, and postmenopausal periods. Since there was no information available as to the physiologic status of the woman with respect to endocrine function and since these periods occur at widely different ages, the changes in blood lipid concentration associated with a given stage in the sexual life cycle may be somewhat masked. The results, however, clearly show that the lower concentration of female than of male serum cholesterol observed in the younger age groups has disappeared by age 50, and that in the older age groups the

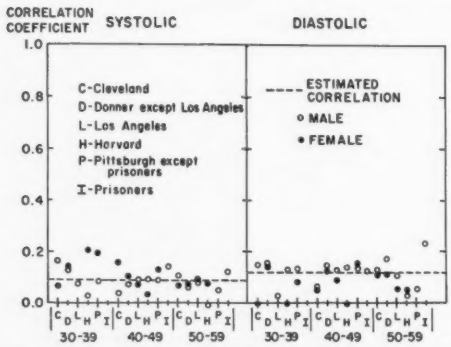

FIG. 13. Correlation of S_f 20–100 and blood pressure by age, sex, and laboratory. (Each point represents a correlation for a single age group within a specific laboratory. Correlations based on less than 20 cases omitted. Each estimated correlation based on all the indicated points.)

concentration in the female is significantly higher than in the male.

Lipid Level and Blood Pressure

The correlation of blood pressure with lipid level calculated from the data for this study is very low. For the various lipids the correlations with systolic and diastolic blood pressures were as follows:

	Systolic	Diastolic
S_f 12–20	.03	.06
S_f 20–100	.09	.12
Cholesterol	.07	.08

(These correlations may be treated as approximately normal deviates with a standard error less than .011. This means, among other things, that they are all significantly greater than zero.)

The correlations presented above are "averaged" from a large number of separate correlations. Because of the differences in mean value by age, sex, and laboratory, correlations were calculated separately for each subgroup. As may be judged from the data for S_f 20–100 (fig. 13), the differences exhibited by these sets of correlations were of a random nature, and they were therefore combined for men and women from all sources between the ages of 30 and 59. The statistical procedure is described in the literature on this subject.[13]

With correlations as low as those described in the preceding paragraph significant differences in lipid level can be expected only for large differences in blood pressure. The Cooperative Study did not include individuals with blood pressures greater than 170/100 mm. Hg, but if an arbitrary division is made of the available pressures into low, normal, and high on the basis of diastolic blood pressure, it is evident that there is some rise in lipid levels associated with a rise in blood pressure (table 11). A low blood pressure level, on the other hand, is associated with a low lipid level. The prisoner group were characterized by remarkably low lipid levels. In the age range 40 to 59 their blood pressure was 115/71 mm. Hg, in contrast to an average pressure of 125/79 mm. Hg for men in this age range from all other Pittsburgh sources. It may be presumed that if the Cooperative Study had included a representative group with blood pressures in excess of 170/100 mm. Hg, they would have exhibited higher lipid levels than the actual study group.

Thus, although the correlations between lipid level and blood pressure are rather weak, large differences in blood pressure levels are associated with differences in lipid level. This is especially true for S_f 20–100, which has the highest correlation with blood pressure. However, it should be emphasized that the differences in lipid level associated with differences in blood pressure are very slight, especially when compared with the population standard deviations given in table 3. While they are manifest for large groups, they have little meaning for individual cases.

Lipid Level and Weight

Since there is a positive correlation between blood pressure and weight, it should be expected that weight and lipid level are related in somewhat the same fashion as blood pressure and lipid level. It is pertinent in this connection to examine the correlation of weight and lipid level.

Within each sex and age group, separate correlations were calculated for each inch of height and each laboratory group. This was done because differences in height were associated with differences in mean weight and differences in laboratory group were associated with

TABLE 11.—*Mean Lipid Levels according to Diastolic Blood Pressure,* Men 40 to 59 (Levels in mg. per 100 ml. Serum)*

Specified source group	S_f 12-20			S_f20–100			Cholesterol		
	Low	Normal	High	Low	Normal	High	Low	Normal	High
Cleveland	32.9	33.5	33.4	76.2	83.5	90.8	238.0	241.8	242.0
Donner except Los Angeles	41.6	47.8	47.6	83.4	105.2	125.1	227.2	241.1	244.2
Los Angeles	53.1	54.6	60.7	69.1	83.0	88.8	260.0	264.1	265.2
Harvard	39.2	39.0	40.7	83.7	83.1	95.0	241.8	240.5	251.2
Pittsburgh except prisoners	42.7	45.2	43.9	81.7	102.2	114.2	230.4	239.3	248.6
Prisoners	31.4	37.7	—	81.6	102.2	—	210.6	218.8	—

* Low diastolic blood pressures are those less than 67, normal are between 67 and 91, high are 92 or more. The average blood pressures for each of these groups were 108/61, 124/80, and 145/96, respectively.

Note: A simple test of these data for a rise in lipid level with blood pressure is the following: Discarding the data for prisoners, take each set of 3 mean lipid levels as a rank sequence. Thus, the sequence of S_f 12–20 levels for Cleveland would be 132. The probability of a sequence 123, that is, of a strict sequence of lipid level from low to high in accord with blood pressure, is 1/6. Actually, 9 out of the 15 sequences are in the order 123. Furthermore, to labor an obvious point, in every sequence the lipid level associated with high blood pressure is higher than the level associated with low.

TABLE 12.—*Correlation of Weight and Lipid Level, all Sources, all Heights*

Sex and age group	Correlation		
	S_f 12–20	S_f 20–100	Cholesterol
Men			
30–39	.16	.23	.14
40–49	.18	.24	.12
50–59	.11	.21	.03
Women			
30–39	.14	.20	.10
40–49	.13	.14	.07
50–59	.03	.16	.01

Note: No correlation based on less than 414 degrees of freedom. The correlations may be treated as approximately normal deviates with a standard error less than .050 for women and .026 for men. All correlations are significantly greater than zero except the one for cholesterol among men 50 to 59 and those for S_f 12–20 and cholesterol among women 50 to 59.

differences in mean lipid level. A test was then made of each group of correlations and it was determined that the differences in correlation attributable to height and source were of a random nature. The specific correlations were therefore combined into the correlations shown in table 12. The statistical procedure is the same as that employed in the preceding section. The correlation of lipid level with weight is highest for S_f 20–100 and lowest for cholesterol. The correlations are slightly higher for men than for women, and are higher between 30 and 49 than from 50 to 59 years of age. These differences, while they are statistically significant, are not impressive, since none of the correlations shown is higher than .24.

To supplement this analysis an overweight group was contrasted with a group of normal weight. The overweight group, in this instance, was defined as that 20 per cent of the men or the women at each inch of height who weighed the most. While this is a neutral and self-contained criterion, it led, in fact, to nearly the same group as would have been defined as 10 per cent or more above their ideal weight according to the Metropolitan Life Insurance Company tables.

Lipid levels are higher in the overweight group than in the group of normal weight by the following percentages:

	Per cent of Elevation in Overweight Group		
	S_f 12–20	S_f 20–100	Cholesterol
Men			
30–39	12	29	4
40–49	17	41	3
50–59	6	17	0
Women			
30–39	12	31	4
40–49	12	24	2
50–59	11	34	1

(When tested individually, all elevations are significant at a 5 per cent level, except the cholesterol elevations for men 50 to 59 and for women 40 to 49 and 50 to 59. However, even for cholesterol, if all 6 elevations are considered together—by combining probabilities from the 6 tests of significance—the elevation is statistically significant at a level of .001, even though it is quite obviously trivial.)

As would be expected, even with correlations as low as those reported, the overweight group had mean lipid levels that were significantly higher, in most instances, than the group of normal weight. Thus, while there is in general only a slight correlation between lipid level and weight, overweight as such is associated with some elevation of lipid levels, although the elevation of cholesterol is negligible.

Summary

Measurements of S_f 12–20, S_f 20–100, and total serum cholesterol made on 10,690 men and 3,404 women are reported and the relation of lipid level to race, source, age, sex, blood pressure, and weight is described. Distributions for men 40 to 59 are reported in detail.

The groups studied, while not selected as representative of the population at large, were remarkably similar in their lipid levels. The lipid levels of only 2 of the 33 groups—Los Angeles and the prisoners—differed significantly from the average. No convincing explanation for either of these exceptions was discovered.

The data in this study were mainly from a white population. Data for nonwhites came primarily from 2 aberrant groups and were too meager to allow a clear characterization of lipid levels. The levels for nonwhites from these 2 sources were closer to those of the white members of these groups than to the levels of the general population.

Cholesterol levels for men and women were found to be about the same at age 20. For both sexes the level rises with age but at first the rise is much greater for men than women. Above age 50, however, the level is higher for women than men and the level for women continues to rise after that age—at least within the age series for this study. The level for men reaches a peak at age 55, after which it declines. The relation of age and sex with lipid level for S_f 12–20 and S_f 20–100 appeared to be similar to that for cholesterol.

Correlations of lipid levels with blood pressure and weight were positive but very low. Hypertension or obesity, however, is associated with some elevation of lipid levels.

S_f 20–100 was found to be the most sensitive of the 3 lipid measures to sex and race differences. In the age group 40 to 59 it was the only one that exhibited a definite race and sex differential. In addition, it had the highest correlation with weight and with blood pressure.

Summario in Interlingua

Es reportate le mesurationes facite de S_f 12 a 20, S_f 20 a 100 e de cholesterol total in le sero de 10.690 homines e 3.404 feminas. Es describite le relation inter le nivello de lipidos e datos de racia, origine, etate, sexo, pression sanguinee, e peso. Le distributiones pro homines de etates de inter 40 e 59 es reportate in detalio.

Le gruppos studiate, ben que non seligite como representante le population general, esseva marcatemente simile in lor nivellos lipidic. Le nivellos lipidic de solmente 2 del gruppos—un gruppo ab Los Angeles e un gruppo de prisioneros—differeva significativemente ab le valores medie. Nulle explication convincente esseva trovate pro iste exceptiones.

Le datos in iste studio esseva derivate principalmente ab un population blanc. Le datos pro le non-blancos esseva derivate primarimente ab le 2 gruppos exceptional e esseva troppo magre pro permitter un clar characterisation del nivellos lipidic. Le nivellos in le non-blancos in iste duo gruppos resimilava plus tosto le nivellos in le blancos del misme gruppos que illos del non-blancos del altere gruppo o illos del population general.

Le nivellos de cholesterol trovate al etate de 20 annos esseva quasi identic in homines e feminas. In ambe sexos le nivello se eleva con le etate, e al principio le elevation es plus grande in homines que in feminas. Supra 50 annos de etate, nonobstante, le nivello es plus alte in feminas que in homines, e in feminas le nivello continua elevar se post ille etate, al

minus in le serie de etates reportate in iste studio. In homines le nivello attinge su maximo al etate de 55 annos e postea illo declina. Le relationes inter etate e sexo e le nivellos lipidic es apparentemente simile in le caso de S_f 12 a 20 e S_f 20 a 100 a illos describite in le caso de cholesterol.

Le correlationes inter le nivellos lipidic con le pression sanguinee e le peso esseva positive sed multo basse. Tamen, hypertension e obesitate es associate con un certe grado de elevation del nivellos lipidic.

Inter le 3 mesurationes lipidic describite, illo de S_f 20 a 100 se monstrava (in le caso del population studiate) como le plus sensibile ab varie punctos de vista. In le gruppo de etates inter 40 e 59 annos, illo esseva le sol mesuration que exhibiva un definite differential secundo racia e sexo. Illo habeva in plus le plus alte correlation con peso e pression sanguinee.

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In poetry, in painting, in physics and in all knowledge there is at least one unifying principle, an article of faith: "In every field one can extend the range of human experience and reduce that experience to order"; or to summarize in a cryptogram: "The unknown is knowable, the impossible is possible"; or finally in a single word: "Conquest!" This is the dynamic of the quest for truth. . . .— John Archibald Wheeler. *A Septet of Sibyls: Aids in the Search for Truth.* American Scientist, p. 364, October 1956.

Serotonin and Antiserotonins

I. Their Circulatory, Respiratory, and Renal Effects in Man

By WILLIAM HOLLANDER, M.D., ALAN L. MICHELSON, M.D., AND ROBERT W. WILKINS, M.D.

Serotonin, (5 hydroxy-tryptamine), a naturally occurring compound, is pharmacologically active on intravenous injection in man. It consistently increases the pulse rate but has a variable pressor, depressor, or biphasic effect on the arterial pressure. The mode of action of serotonin on these functions is not clear. Serotonin consistently and characteristically increases ventilation. However, it does not cause striking circulatory changes in the kidney although it usually produces moderate antidiuresis. The benzyl analog of serotonin (BAS) (1-benzyl-2-methyl-3-methoxy-tryptamine), both intravenously and orally, reduces or prevents the symptoms caused by serotonin. Intravenously, BAS in addition has demonstrable "antiserotonin" effects on the characteristic blood pressure and respiratory responses to serotonin.

SEROTONIN, chemically identified as 5-hydroxy-tryptamine, is a naturally occurring compound found mainly in the intestinal mucosa, the platelets, and the brain. Its concentration in the blood is low. The compound is rapidly inactivated by amine oxidase in the tissues and is excreted in the urine as 5-hydroxy-indoleacetic acid. Recently a clinical syndrome of malignant carcinoid of the small intestine with metastases to the liver has been described in which large amounts of serotonin are produced and released by the tumor.[1,2] The physiologic role of serotonin in man is not clear but studies in animals suggest that the compound might participate in the regulation of hemostasis, arterial tone, renal function, and mental processes.[3,4]

To evaluate some of the possible functions of serotonin in man, its effects on blood pressure, respiration, and kidney function were studied after intravenous injection in subjects with and without arterial hypertension. Various types of blocking drugs (adrenergic, cholinergic, ganglionic, antihistaminic) and, in addition, one analog of serotonin, 1-benzyl-2-methyl-5-methoxy-tryptamine (BAS, Woolley*),[5] were tested to determine their effectiveness as pharmacologic antagonists to serotonin.

METHODS

Arterial blood pressure responses to serotonin creatinine sulfate† were studied in 20 normotensive and 35 hypertensive subjects without heart failure. Most of the subjects were tested with single intravenous injections of serotonin given in increasing doses ranging from 0.25 to 2 mg. at intervals of at least 10 minutes. The effect of a given dose of serotonin on the blood pressure was also studied before and after the administration of phentolamine (Regitine), hexamethonium, atropine, pyrilamine (Neo-Antergan), diphenhydramine hydrochloride (Benadryl), reserpine, and BAS. The blood pressure was measured through an indwelling brachial artery needle with an electromanometer recording by direct-writing oscillograph. Respiratory responses to the same doses of intravenous serotonin were also studied in 30 of the subjects. Tidal and minute volumes were measured through a closed spirometric system recording on a rotating drum.

Renal responses to serotonin or to BAS were studied in 23 subjects lying supine in the postabsorptive state. Renal function was measured by methods previously described.[6] Following the control period, during which time 3 or 4 10- or 15-minute urine collections were obtained, serotonin in a single dose of 1 mg. was injected rapidly through an indwelling intravenous needle. Following the injection, several urine collections were made, each over a period of 10 to 15 minutes. The first 3 of these collections were designated the "serotonin period," since this was the time during which serotonin effects on renal function were usually observed. The subsequent urine col-

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* Obtainable from Merck Sharp & Dohme Research Laboratories, Rahway, N. J.

† Kindly supplied by the Upjohn Company, Kalamazoo, Mich.

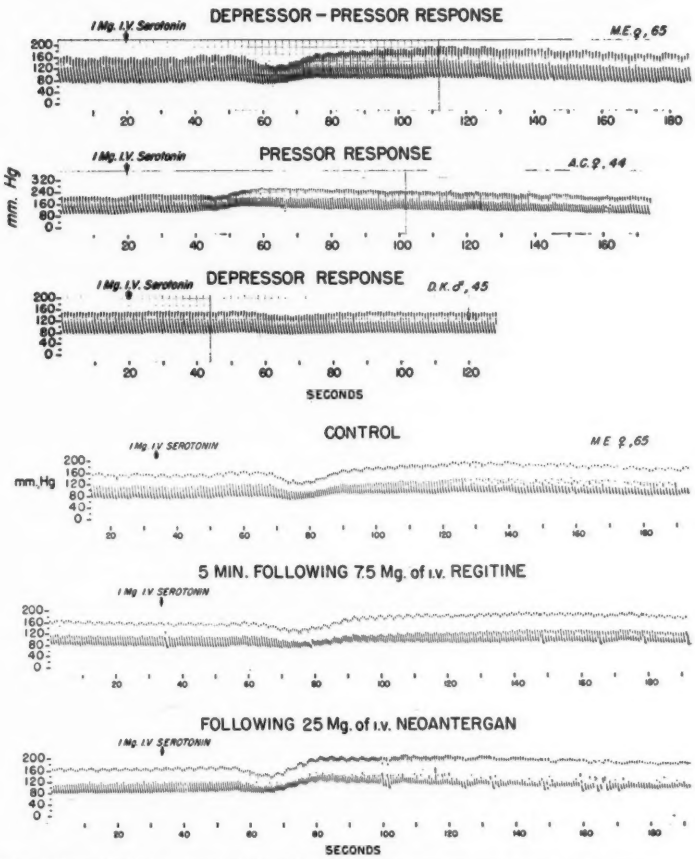

FIG. 1 *Top*. Characteristic types of brachial artery pressure responses to intravenous serotonin.

FIG. 2 *Bottom*. The effect of Regitine and Neo-Antergan on the arterial pressure responses to serotonin. Regitine in doses that produced adrenergic blockade was without effect (second tracing) but Neo-Antergan increased the pressor effect of serotonin (lowest tracing).

lections, 3 or more, were designated the "recovery period," since the renal effects of serotonin were then usually no longer apparent.

In 7 subjects a single intravenous injection of BAS was given after the control period or after the administration of serotonin. In either case, the direct effect of BAS on renal function was followed for at least 3 15-minute periods ("BAS period") before its "blocking effects" on serotonin action were tested by repeating the standard test dose (1 mg.) of serotonin intravenously.

RESULTS

Blood Pressure Responses to Intravenous Serotonin

Serotonin, infused at a rate of 1 to 2 ml. per minute, in a concentration of 10 to 25 μg. per ml., produced no significant effects on the blood pressure or pulse rate in 6 subjects. However, it did produce intense spasm of the infused vein, which limited the rate of infusion of serotonin. In 3 subjects, as venospasm developed, the infused vein became prominent, firm, and tender, and the entire extremity turned cyanotic.

In contrast to such an infusion, single intravenous injections of serotonin in doses of 0.25 to 2 mg. produced definite but variable effects on the blood pressure. The 3 characteristic types of brachial arterial pressure response (1, depressor; 2, depressor-pressor; 3, pressor) are shown in figure 1. They occurred in both

hypertensive and normotensive individuals with about equal frequency.

Depressor Response. Of the 3, the depressor response occurred most often after doses of serotonin less than 0.75 mg. It was characterized by reductions in the systolic and diastolic blood pressures of 10 to 30 mm. Hg. The changes in blood pressure lasted for 15 to 90 seconds and were accompanied by increases in the pulse rate of 5 to 40 beats per minute.

Depressor-Pressor Response. The depressor-pressor or biphasic response, occurred more frequently when the dose of serotonin was increased to over 0.5 mg. It was characterized first by a brief fall in the blood pressure followed by an overshoot that lasted for 1 to 5 minutes. The changes in systolic and diastolic blood pressure ranged from 10 to 40 mm. Hg. Both the depressor and pressor components of this response were accompanied by increases in the pulse rate of 5 to 40 beats per minute.

Pressor Response. The pressor response occurred with increased frequency as the dose of serotonin was increased toward 2 mg. It was characterized by an increase in the blood pressure and pulse rate that lasted for 1 to 6 minutes. The increase in systolic and diastolic blood pressure ranged from 10 to 50 mm. Hg and the rise in pulse rate from 5 to 50 beats per minute. The response, like those previously described, occurred 15 to 45 seconds after the injection of serotonin and showed no diminution on repeated injections given at intervals of more than 10 minutes.

Serotonin produced mild to severe symptoms in three quarters of the 55 subjects tested. These symptoms lasted for 1 to 3 minutes and most commonly consisted of anxiety, dizziness, tingling of the extremities, substernal pressure, abdominal cramps, back pain, cough, and shortness of breath.

Effect of Various Drugs on the Brachial Arterial Pressure Responses to Serotonin

Autonomic-Blocking Drugs (Regitine, hexamethonium, atropine). Regitine (phentolamine) given to 6 subjects in intravenous doses of 5 to 10 mg. failed to block completely the pressor action of 0.5 to 1 mg. of intravenous serotonin (fig. 2). However, in 3 of the subjects Regitine reduced the pressor response to serotonin by 10 to 15 mm. Hg although it had no effect on the depressor effect.

Hexamethonium given intravenously to 5 subjects in hypotensive doses of 10 to 30 mg. did not alter the pressor or the depressor response to 0.5 to 1 mg. of intravenous serotonin (fig. 3). The doses of hexamethonium administered produced ganglionic blockade as indicated by the appearance of postural hypotension and a "sympathectomy" type of brachial arterial pressure response to the Valsalva maneuver.[7] Intravenous atropine in doses of 0.5 to 1 mg. likewise had no effect on these responses in 5 subjects.

Antihistaminic Drugs [Neo-Antergan (pyrilamine maleate), Benadryl (diphenhydramine hydrochloride)]. In 4 of 5 subjects Neo-Antergan in intravenous doses of 20 to 25 mg. strikingly increased the pressor effect of 0.5 to 1 mg. of intravenous serotonin by 10 to 40 mm. Hg. In 3 to 4 subjects Benadryl in intravenous doses of 20 mg. produced the same result.

In addition, both antihistaminic drugs slightly decreased the depressor action of serotonin. A characteristic effect of Neo-Antergan on the brachial arterial pressure responses to serotonin is shown in figure 2.

Reserpine. In 4 subjects neither the depressor nor the pressor effects of 0.5 to 1 mg. of intravenous serotonin were altered by intravenous reserpine in doses of 1 to 2.5 mg. The brachial arterial pressure responses to serotonin were recorded frequently during 4 to 6 hours, and also 12 and 24 hours, after the administration of reserpine, but they did not change.

Oral reserpine administered for 1 to 3 months in daily hypotensive doses of 0.5 to 1 mg. to 5 hypertensive subjects likewise failed to alter the brachial arterial pressure responses to 0.25 to 2 mg. of intravenously injected serotonin except in 1 subject. This one individual had a greater *depressor* response to 5 mg. of intravenous serotonin after than before reserpine treatment.

BAS (1-benzyl-2-methyl-5-methoxy-tryptamine). In 5 of 22 subjects tested, BAS in intravenous doses of 50 to 150 mg. completely blocked the pressor but not the depressor effect of 0.5

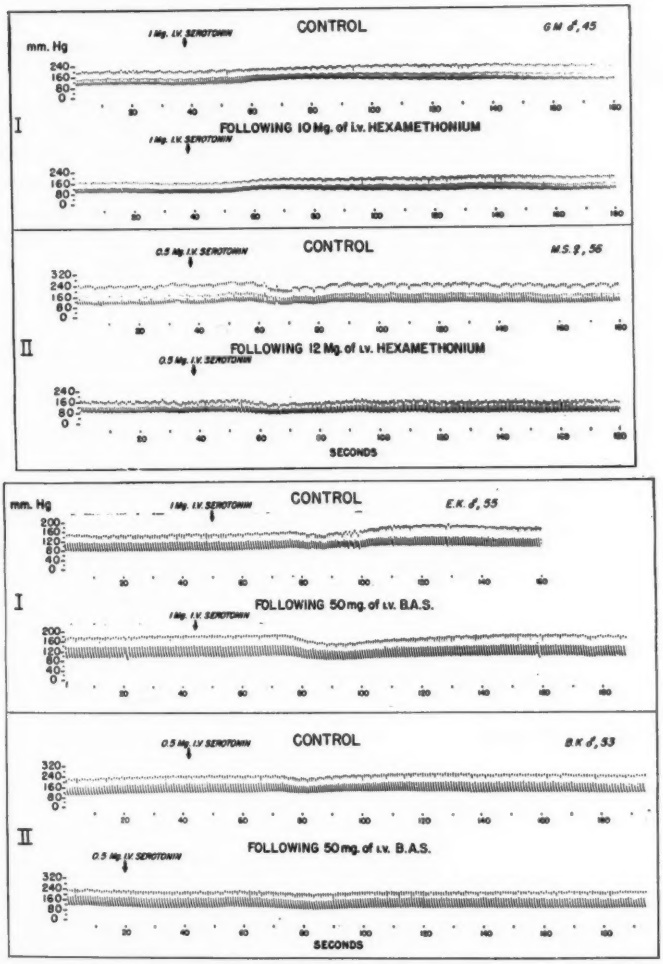

FIG. 3 *Top.* The effect of hexamethonium on the arterial pressure response to serotonin. Hexamethonium in doses that produced ganglionic blockade did not alter the pressor effect of serotonin (upper tracings) or the depressor effect of serotonin (lower tracings).

FIG. 4 *Bottom.* The effect of BAS (1-benzyl-2-methyl-5-methoxy-tryptamine) on the arterial pressure responses to serotonin. As shown in the upper tracings, subject E. K. had a depressor-pressor response to serotonin in the control period. After intravenous BAS the pressor component of the response disappeared but the depressor component persisted and became prolonged. A similar but less striking effect of BAS is shown in the lower tracings.

to 1 mg. of intravenous serotonin (fig. 4) for at least 30 to 60 minutes. The depressor effect of serotonin not only persisted but also was prolonged after the administration of BAS in 3 of these 5 subjects, all of whom showed a depressor-pressor response to serotonin during the control period.

In 7 of the 22 subjects tested, BAS in intravenous doses of 50 to 175 mg. partially blocked the pressor effect of serotonin. The rise in blood pressure caused by serotonin was 10 to 30 mm. Hg less after than before the administration of BAS. In the remaining 10 subjects, the blood pressure responses to serotonin were not strikingly altered by 25 to 100 mg. of BAS. However, in all 22 subjects BAS consistently

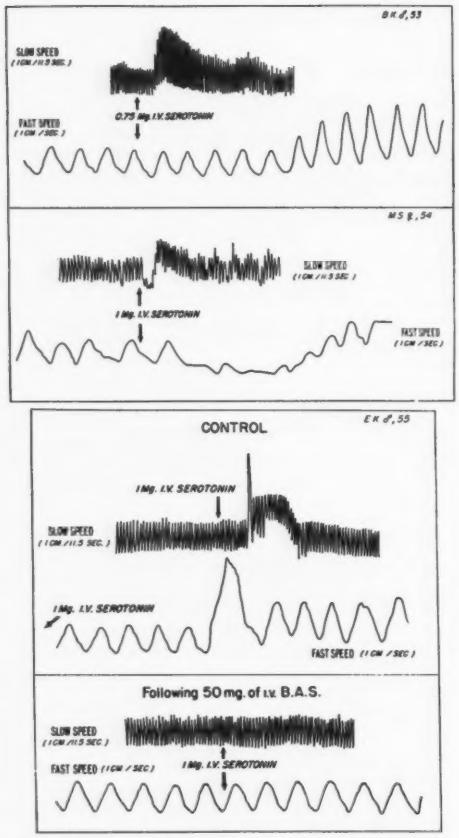

FIG. 5 *Top.* Characteristic respiratory responses to serotonin. As indicated in lower tracings, a period of apnea occasionally preceded the hyperventilation caused by serotonin.

FIG. 6 *Bottom.* The effect of intravenous BAS on the respiratory responses to serotonin. The hyperventilation produced by serotonin (upper tracing) was completely blocked by BAS (lower tracing).

reduced or eliminated the symptomatic side effects produced by serotonin.

BAS given orally to 5 hypertensive subjects in hypotensive doses of 30 to 100 mg. a day for 1 to 2 months failed to alter the pressor or the depressor action of 0.5 to 1.5 mg. of intravenous serotonin. However, oral BAS like intravenous BAS partially or completely blocked the symptoms caused by serotonin.

Respiratory Responses to Intravenous Serotonin

The upper tracing in figure 5 shows a typical respiratory response to intravenous serotonin. This response, which occurred in 25 of 30 subjects, was characterized by an increase in the depth and rate of respiration together with an elevation of the mid position of chest that lasted from 30 seconds to 2 minutes. The hyperventilation produced by serotonin was frequently accompanied by subjective shortness of breath, occasionally with coughing, but without wheezing. In a few subjects, as illustrated in the lower tracing of figure 5, an apneic period of 15 to 30 seconds preceded the phase of hyperventilation.

The hyperventilation and dyspnea caused by serotonin did not necessarily depend upon increases in pulmonary arterial pressure. All 3 subjects, in whom pulmonary arterial pressure and respiratory responses to serotonin were simultaneously measured, developed tachypnea and shortness of breath without a rise in the pulmonary artery pressure.

Effect of BAS on the Respiratory Responses to Intravenous Serotonin. BAS in intravenous doses of 50 to 150 mg. appeared to be more effective in blocking the respiratory response than it was in blocking the blood pressure responses to intravenous serotonin. In 15 of 20 subjects intravenous BAS blocked the respiratory effects of serotonin either completely or almost completely. The blocking action of BAS is illustrated in figure 6. On the other hand, oral BAS given to 5 subjects in doses of 40 to 100 mg. a day for 1 month did not prevent the respiratory responses to intravenous serotonin.

Renal Effects of Intravenous Serotonin

The renal responses to intravenous serotonin are summarized in table 1. The mean data and statistical analyses of the responses are presented in table 2.

Urine Flow. Following the administration of serotonin, urine flow was reduced moderately but significantly (fig. 7). It returned to or toward the control flow in 45 minutes on the average. A decrease in urine flow occurred not only in subjects who had experienced symptoms from the serotonin but also in those who had no symptoms. Changes in urine volume after serotonin were inconsistently related to changes in blood pressure or in inulin clearance.

Renal Hemodynamic Function and Electro-

TABLE 1.—*Effects of Intravenous Serotonin (1 mg.) and BAS on Renal Function in Subjects with Arterial Hypertension*

Patient, age, sex	Procedure	C_{PAH} ml./min./1.73 M.²	C_{IN} ml./min./1.73 M.²	UV ml./min.	$U_{Na}V$ MicroEq./min.	$U_{K}V$ MicroEq./min.
M. S., 54, F	Control	303	76	6.6	554	86
	Serotonin	311	70	2.4	332	85
	Recovery	324	73	4.0	423	79
M. B., 35, F	Control	540	119	3.3	535	89
	Serotonin	454	106	2.9	338	59
	Recovery	524	123	5.4	360	65
M. K., 35, F	Control	473	128	6.8	391	152
	Serotonin	383	105	4.3	343	127
	Recovery	473	123	6.4	457	151
A. C., 50, F	Control	393	88	7.9	573	98
	Serotonin	379	81	4.4	518	104
	Recovery	492	96	8.2	450	138
A. T., 55, F	Control	454	98	8.0	408	86
	Serotonin	443	101	2.7	338	77
	Recovery	472	101	5.0	361	82
C. L., 65, M	Control	228	76	4.3	313	116
	Serotonin	216	76	4.0	250	107
T. L., 63, M	Control	216	65	6.3	92	38
	Serotonin	214	67	7.0	139	50
E. K., 65, M	Control	392	82	7.1	153	88
	Serotonin	356	71	2.7	128	74
	Recovery	388	80	3.0	135	76
T. B., 46, F	Control	561	113	6.4	26	88
	Serotonin	408	83	1.5	8	46
	Recovery	569	118	3.2	11	65
H. L., 43, F	Control	604	125	6.4	270	112
	Serotonin	453	112	2.3	164	77
	Recovery	552	107	1.3	127	77
H. L.,* 44, F	Control	675	141	7.2	332	160
	Serotonin	552	110	5.1	185	92
	Recovery	655	127	9.8	267	100
M. S., 54, F	Control	86	24	4.3	134	54
	Serotonin	66	19	2.1	103	47
M. S.,* 54, F	Control	93	24	5.2	174	45
	Serotonin	69	19	2.2	111	34
	Recovery	92	26	4.2	150	43
B. K., 51, M	Control	344	84	8.6	114	77
	Serotonin	291	83	8.3	200	82
	BAS (50 mg.)	257	78	8.2	201	75
	Serotonin	253	81	4.5	176	89
B. K.,* 52, M	Control	311	89	7.6	234	53
	Serotonin	242	81	2.5	253	64
	Recovery	250	87	5.7	380	65
O. J., 51, M	Control	685	148	5.8	127	34
	BAS (40 mg.)	659	152	7.8	165	37
	Serotonin	449	134	6.6	157	40
O. J., 51, M	Control	572	135	5.8	48	35
	Serotonin	625	139	8.3	61	31
	Recovery	634	145	6.3	74	35
	BAS (50 mg.)	635	144	3.5	89	32
	Recovery	637	140	2.7	78	34
B. R., 32, F	Control	603	102	5.9	71	110
	Serotonin	563	91	2.9	71	97
	Recovery	621	101	4.1	94	100
	BAS (20 mg.)	553	90	2.4	98	83

TABLE 1—*Continued*

Patient, age, sex	Procedure	C_{PAH} ml./min./1.73 M.²	C_{IN} ml./min./1.73 M.²	UV ml./min.	$U_{Na}V$ MicroEq./min.	$U_{K}V$ MicroEq./min.
B. R., 32, F	Control	599	107	9.4	67	67
	BAS (20 mg.)	538	96	5.5	80	66
	Recovery	589	110	7.3	93	71
	Serotonin	567	110	7.3	92	69
	Recovery	560	112	8.2	108	68
J. W., 46, M	Control	181	28	5.5	234	82
	Serotonin	149	25	2.5	146	79
	Recovery	157	26	3.4	168	103
	BAS (15 mg.)	152	25	3.9	134	113
	Serotonin	118	20	1.7	53	88
M. S., 48, M	Control	284	69	6.6	302	64
	Serotonin	254	69	4.8	337	65
	Recovery	289	74	7.7	529	87
	BAS (15 mg.)	277	74	5.7	582	103
	Serotonin	280	76	7.5	669	110
N. B., 46, M	Control	490	98	5.5	116	86
	Serotonin	421	90	4.7	121	81
	Recovery	478	98	5.4	146	81
	BAS (20 mg.)	425	94	5.4	139	72
	Serotonin	407	95	4.9	144	70
R. W., 55, F	Control	494	94	9.1	234	107
	Serotonin	426	88	4.3	251	98
	Recovery	439	91	5.9	254	90
	BAS (50 mg.)	391	90	5.8	432	81
	Serotonin	371	92	5.2	478	88

*Restudied after oral BAS treatment.

lyte Excretion. The measurements of renal plasma flow (PAH clearance) and glomerular filtration rate (inulin clearance) and the excretion of sodium and potassium were slightly but significantly reduced following the injection of serotonin. Since these measurements generally changed in the same direction as urine flow, they might not have been due to actual reductions in renal hemodynamic function or electrolyte excretion but to inadequate washout of "dead space" because of the reduction in urine flow. However, in some instances, the reductions in these functions appeared to be real, since they occurred without a similar change in urine flow.

Renal Effects of Intravenous BAS. The effect of BAS on renal function is included in table 1. As with serotonin, BAS in 4 of 9 tests produced a reduction in urine flow which was irregularly accompanied by a reduction in the PAH and inulin clearances and electrolyte excretion (fig. 7). The ability of BAS in intravenous doses of 15 to 50 mg. to block the renal effects of serotonin was not striking. Only in subject B.R., who was studied on 2 separate occasions, were the findings definitely suggestive of a blocking action by BAS on the renal effects of serotonin.

Oral BAS given to 3 subjects (H. L., M. S., and B. K.) in daily doses of 60 mg. for 1 month did not alter renal hemodynamic function at rest. It likewise did not appear to prevent the effects of intravenous serotonin on renal function.

Discussion

Serotonin injected intravenously had a variable effect on the blood pressure but it consistently increased the pulse rate. In small doses it usually reduced the blood pressure whereas in larger doses it frequently caused an increase with or without an antecedent decrease. The manner in which serotonin affected the arterial pressure was not clear. Animal studies suggest that the blood pressure effects of serotonin are largely mediated through the autonomic nerv-

TABLE 2.—*Mean Data and Statistical Analysis*

	Control	Serotonin	Difference*	Recovery	Difference†
			C_{PAH}		
Mean	395	346	−49	436	−0.8
SE	±38	±34	±11	±40	±10
p			<.01		>.9
			C_{IN}		
Mean	88	80	−8	94	−0.8
SE	±7	±7	±2	±8	±2
p			<.01		.7
			UV		
Mean	6.4	3.9	−2.5	5.2	−1.3
SE	±0.3	±0.4	±0.5	±0.5	±0.5
p			<.01		.03
			$U_{Na}V$		
Mean	253	209	−43	258	−16
SE	±36	±27	±17	±38	±25
p			.02		0.5
			$U_{K}V$		
Mean	87	75	−12	84	−6
SE	±7	±5	±4	±7	±5
p			.01		0.3

* Difference between control and serotonin measurements.

† Difference between control and recovery measurements.

ous system. In man, however, the mode of action appears to be different, since autonomic blocking agents such as intravenous hexamethonium, Regitine, and atropine failed to alter the blood pressure responses to serotonin significantly. The finding that the blood pressure responses to serotonin were markedly affected by antihistaminic drugs might be interpreted to indicate that they result in part from a histamine-releasing action of serotonin. However, the effects of antihistaminic drugs on the blood pressure may not necessarily be related to a histamine blocking action. Thus, as the studies of Tickner[9] suggest, they may result from an inhibitory action of antihistaminic drugs on aminoxidize, which normally converts serotonin to inactive 5-hydroxy-indoleacetic acid.

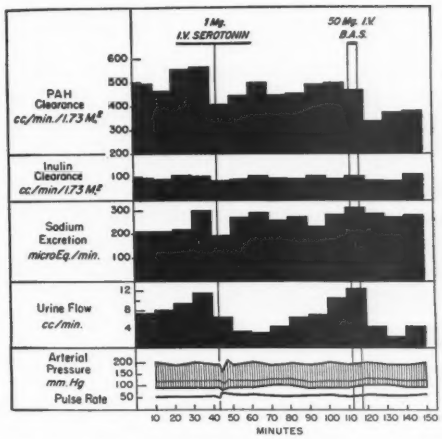

FIG. 7. Renal responses to intravenous serotonin and BAS in a hypertensive individual. Serotonin caused a moderate reduction in urine flow without producing a striking change in renal plasma flow, glomerular filtration rate, or sodium excretion. BAS likewise caused a reduction in urine flow that was accompanied by a decrease in renal plasma flow but not in glomerular filtration rate and sodium excretion.

Studies in animals indicate that reserpine reduces the body stores of serotonin.[10] Therefore, it was conceivable, since serotonin affects arterial pressure, that the hypotensive action of reserpine is mediated through its effect on serotonin metabolism. However, no conclusive evidence for this hypothesis was obtained from the present pharmacologic study, which showed that reserpine, administered orally or intravenously, had no significant effect on the blood pressure responses to intravenous serotonin except in 1 subject. Perhaps more sensitive biochemical studies will reveal a more definite causal relationship between the hypotensive and metabolic effects of reserpine.

The benzyl analog of serotonin, (BAS) synthesized by Drs. Woolley and Shaw,[5] was capable of blocking the blood pressure and respiratory responses to serotonin and therefore was considered to be a definite antiserotonin compound. However, in the doses used it did not consistently block the pharmacologic effects of serotonin. When administered orally, BAS had no demonstrable antiserotonin activity on the blood pressure or respiration but did partially

or completely prevent the symptoms produced by intravenous serotonin.

Serotonin, in intravenous doses of 1 mg., had a definite but moderate antidiuretic effect that appeared to be due directly to serotonin itself. However, in those subjects with disturbing side reactions from serotonin, emotional factors might have operated to cause an antidiuresis. The reduction in urine flow caused by serotonin did not appear to be due to an effect of serotonin on the blood pressure, since it occurred with either an increase or a decrease in blood pressure. Evidence that serotonin also has a vasoconstrictor and salt-retaining action on the kidney was not conclusive in this study. Although slight reductions in renal plasma flow, glomerular filtration rate, and the excretion of sodium and potassium appeared to follow the administration of serotonin, they might have been due in part to decreases in urine flow. Reductions in renal hemodynamic function and electrolyte excretion appeared to be real in some cases, however, since they occurred without similar changes in urine flow. Nevertheless, even in these subjects the renal vasoconstrictor and salt-retaining effects of serotonin were weak.

Summary

Serotonin, injected intravenously, had a variable depressor or pressor action on the arterial pressure, but it consistently increased the pulse rate. The effects of serotonin on the blood pressure may be in part direct, since no definite evidence was found to indicate that they were mediated through the autonomic nervous system. Serotonin consistently produced hyperventilation that was frequently accompanied by dyspnea. It likewise acted as a moderate antidiuretic, but a weak renal vasoconstrictor.

Intravenous benzyl analog of serotonin (BAS) was capable of blocking not only the symptoms but also the increases in blood pressure and respiration caused by intravenous serotonin. Oral BAS, however, had no demonstrable antiserotonin activity on the blood pressure or respiration although it did reduce the side reactions caused by serotonin.

Summario in Interlingua

Injectiones intravenose de serotonina habeva un variabile effecto depressori o pressori super le pression arterial sed resultava uniformemente in un acceleration del pulso. Le effectos de serotonina super le pression sanguinee es forsan in parte de natura directe, proque nulle observationes esseva facite que indicarea que ille effectos esseva mediate via le systema nervose autonome. Serotonina produceva uniformemente hyperventilation que esseva frequentemente accompaniate de dyspnea. Serotonina etiam ageva como un moderate antidiuretico, sed illo esseva debile como vasoconstrictor renal.

Le injection intravenose del analogo benzylic de serotonina (ABS) esseva capace a blocar non solmente le symptomas sed etiam le augmentos de pression sanguinee e de respiration causate per serotonina in administration intravenose. Tamen, ABS oral habeva nulle demonstrabile activitate antiserotoninic manifeste in le pression sanguinee e le respiration, sed il es ver que illo reduceva le reactiones lateral causate per serotonina.

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Experimental myocardial embolization produced in dogs by the injection of plastic spheres was employed to examine the circulatory, pathologic, and biochemical alterations that followed myocardial infarction. The media employed for the injections into the coronary circulation included gum acacia, human albumin, and dog plasma. Among the measurements obtained were blood gases; blood glucose pyruvate, lactate, and ketone bodies. Plasma enzyme measurements included transaminases, aldolase, isomerase, and inalic dehydrogenase. Cardiac output and blood pressure determinations were recorded. Histopathologic data were studied at specific intervals from 20 minutes to 6 weeks following embolization.

The injection of spheres suspended in gum acacia resulted in decreased cardiac output, diminished coronary flow and myocardial oxygen consumption of more severe degree than occurred with dog plasma or human albumin. The latter substances apparently led to coronary vasodilatation, possibly of reflex origin. The myocardial extraction and utilization of lactate, pyruvate and ketones was immediately lowered following myocardial embolization. The extraction and consumption of glucose were less diminished due to the fact that anaerobic glycolysis could still proceed under these conditions. These changes appeared to be rapidly reversible. The plasma activity of the enzymes rose within 2 hours after embolization reaching a peak within 24 hours correlating with the height of coagulation necrosis of the infarcted myocardium. The pathologic changes consisted of a coagulative necrosis followed by polymorphonuclear infiltration reaching its peak in 2 or 3 days. The reparative phase marked by fibroblasts and mononuclear cells became well developed within 6 days. Cellularity diminished as collagen formation and fibrillary tissue was developed in the lesions.

A correlation of the data indicated that myocardial ischemia produced a period of decompensation of the affected heart muscle with a decrease in cardiac output and blood pressure. There were transient changes in substrate utilization and an increase in anaerobic activity of the heart muscle. The localized response appeared to be that of a coronary vasodilatation. Immediately thereafter, the muscle showed evidence of cellular necrosis the height of which coincided with the peak of plasma enzyme activity. This activity declined as reparative processes in heart muscle occurred.

SHUMAN

Serotonin and Antiserotonins

II. Clinical Studies, Especially in Essential Hypertension with the Benzyl Analog of Serotonin (BAS)

By ROBERT W. WILKINS, M.D., AND WILLIAM HOLLANDER, M.D.

Serotonin, a smooth-muscle constrictor, has been suggested as possibly important in the pathogenesis of arterial hypertension. The benzyl analog of serotonin (BAS) was developed as an antimetabolite of serotonin, and has certain demonstrable antiserotonin effects in man. Orally it has moderate antihypertensive and other clinical effects resembling those of reserpine, which also has a definite antiserotonin action. However, there is question whether the clinical effects of oral BAS or of reserpine in hypertension are due to "antiserotonin" or other pharmacologic actions. BAS is clinically useful in the therapy of some patients with essential hypertension.

WHAT role, if any, serotonin (5 hydroxytryptamine) may play in the pathogenesis of essential hypertension is open to question.[1] Although admittedly often pressor when given in large dosages intravenously, the effects of serotonin on blood pressure are always variable.[2–5] Indeed, when given intravenously it does not cause a generalized vasoconstriction characteristic of the hypertensive state, but rather produces vasoconstriction in some vascular areas, for example, in the kidney, and vasodilatation in others, for example, in the skin. Moreover, the concentration of serotonin is not increased in the plasma of hypertensive patients. Indeed in the one disease in which its concentration may be greatly increased, namely in carcinoid cases, hypertension is not one of the usual clinical features of the syndrome.[6] However, the concentration of serotonin in plasma may not be the critical factor, since it is a readily metabolizable hormone, and its true action may depend more upon its momentary liberation, or activation, in certain local areas, for example, within the brain, than upon its circulation within the blood stream.[7]

Numerous hypotheses have been advanced for the functions of serotonin within the body. These include a styptic or hemostatic function upon its liberation from the platelets of the blood, a tonic function in the bowel upon its liberation by the chromaffin cells of the intestinal wall, a blood pressure-regulating function through its circulation or perhaps its local liberation within the vascular system, and finally a central nervous system-regulating function through its activation within the brain. However, none of these hypotheses is above serious criticism. This is but natural considering that we know, as yet, too little concerning the natural physiology of this material.

Antiserotonins of various chemical types have been known almost since the discovery of serotonin itself. Among the more interesting are the yohimbine alkaloids and the lysergic acid derivatives. In addition numerous simple analogs of serotonin have been synthesized and some have been shown to have antiserotonin activity.[8] Among the latter "antimetabolites," we have been supplied with several for clinical trial, usually by intravenous administration. One of these, BAS, the benzyl analog of serotonin, (Woolley*),[9-10] can be administered by mouth as well as intravenously, and is well tolerated for long-term clinical trial. The present report describes experiences with these analogs in clinical disease states, particularly essential hypertension.

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* Obtainable from Merck Sharp & Dohme Research Laboratories, Rahway, N. J.

Material and Methods

The patients were selected from our clinic and private practice usually because they were known to have hypertension and had been studied well enough and long enough to characterize their hypertension as chronic, relatively fixed, and either uncomplicated or complicated by varying degrees of cardiovascular disease as revealed by a routine study of cerebral, cardiac, renal, and vasomotor systems. These studies always included complete history, physical examination, urine analysis, sedation test, and cold and posture test. Patients were selected for trial on one of the antiserotonin preparations, either alone or in combination with other "antihypertensive" medications.

The first experiment was with the compound, 2-methyl-3-ethyl-5-nitroindole (Woolley), which was given alone by mouth to 6 of the hypertensive patients. In the dosage used (2 Gm. a day), the patients were able to tolerate this medication for only 3 to 8 days and then voluntarily discontinued its use because of side effects of mental depression, insomnia, nausea, diarrhea, and abdominal cramps. There were no significant changes in blood pressure in any patient during the administration of this drug.

In the second experiment the serotonin analog, 1-ethyl-3-(2-dimethyl amino-1-hydroxyethyl)-indole (Upjohn), was given orally to 7 hypertensive subjects in daily doses of 12.5 to 400 mg. Within 1 to 10 days it had to be withdrawn because of its severe side effects of abdominal cramps, diarrhea, chills, flushing, urticaria, and dysesthesia. During treatment no significant change in blood pressure occurred.

Studies with a third antiserotonin, 1-N^1(diphenylacetyl) 1-phenyl-N^1,N^2,N^2,trimethyl-1,2-propanediamine HCl (Hoffmann LaRoche), also had to be discontinued because of disturbing side reactions such as anxiety, confusion, disorientation, dizziness, giddiness, and paresthesias.

Only BAS proved to be well tolerated by mouth over long periods of time. It was given to a total of 70 patients for periods ranging from 2 weeks to 12 months and in amounts ranging from 5 to 200 mg. a day (usually in 4 divided doses). In 45 of these patients, the drug was taken faithfully enough and long enough to allow valid observations of its symptomatic and blood pressure effects. In 25 patients the drug was administered alone, alternating with placebos at varying intervals. In the remaining 20 patients it was given in combination with other hypotensive drugs that had not had the desired clinical effect. The hypertension in these latter cases therefore, might be termed "resistant" to drugs.

Finally in 3 patients* with disseminated carcinoidosis BAS was given in doses up to 100 mg. a day in an effort to combat their symptoms of facial flushing and burning, abdominal cramps, and diarrhea.

Results

Table 1 shows the results of BAS administration in 25 hypertensive patients given the drug alone in alternation with a placebo. The average of the control blood pressures in this group was 201/121 mm. Hg. The average blood pressure during treatment with BAS (average dose, 72 mg. a day for 18 weeks) was 183/110, or about 20/10 mm. Hg lower than the average during the control periods. Furthermore, it is interesting that while the blood pressure was reduced by 20/10 mm. Hg or more in 9 of the 25 patients, it was not reduced at all in 7.

Table 2 shows the effects of BAS when added to a regimen of other hypotensive drugs. These drugs included rauwolfia (or reserpine), veratrum, Apresoline, and occasionally a blocking agent (particularly pentolinium or hexamethonium). The average of the blood pressures before any treatment whatsoever in these patients was 220/124. With the other hypotensive drugs used, the average of the blood pressures was 202/116. When BAS was added to these drugs the blood pressure was 192/109, a negligible decrease in the average. However, it was noted in 6 of these 20 when BAS was added that the blood pressure was reduced by 20/10 mm. Hg or more, while in 11 of the 20 it was not affected in any way.

Figure 1 shows one of the more striking results from the administration of BAS to a hypertensive patient. It demonstrates that the drug had both a hypotensive and a bradycrotic effect as compared with the placebo, and in this patient the medication also had a symptomatically beneficial action. Figure 2 shows the blood pressure effects in another patient given BAS alone as compared with reserpine alone and a combination of BAS with reserpine. The combination of BAS and reserpine had a more definite hypotensive effect than either agent used alone. Figure 3 demonstrates the blood pressure effect of BAS given in combination with 3

* We are indebted to Dr. Malcolm Stanley of the New England Medical Center for the information on 2 of these patients.

TABLE 1.—*BAS, Alone, in Arterial Hypertension*

Patient, age, sex	Control period		Period on BAS			
	Average B.P. mm. Hg	Duration weeks	Average B.P. mm. Hg	Dose of BAS mg./day	Duration weeks	Comments
H. W., 32, F	190/120	32	140/90	80	44	Relaxed, sedated, sleeps better, no headache or palpitation; intermittent nasal stuffiness; diarrhea followed later by constipation
R. W., 52, F	200/110	12		40	1	Stopped treatment because of excessive sedation
J. W., 56, M	210/130	16		40	1	Stopped treatment because of excessive sedation
H. W., 54, M	180/120	22	160/105	100	26	
V. V., 38, F	170/120	26	160/100	40	24	Less palpitation, more relaxed, intermittent nasal stuffiness
B. K., 53, M	250/150	12	230/120	200	24	Sedated and relaxed
G. T., 46, M	180/120	26	160/100	40	24	
M. S., 56, F	260/130	24	210/110	80	32	Sleepy, less palpitation and headache
E. S., 63, F	180/100	18	170/90	80	32	Less palpitation, headache and angina
L. P., 69, F	220/110	24	210/110	40	18	
M. M., 42, F	190/120	16	170/110	40	18	Sleepy, sedated; intermittent abdominal cramps and diarrhea
A. L., 63, M	260/150	12	260/150	200	16	Sedated
H. K., 44, F	200/120	12	180/115	40	16	More relaxed
M. P., 50, F	210/110	12	160/80	40	36	Sedated, relaxed, and intermittent nasal stuffiness
W. M., 42, M	180/130	24	180/130	80	10	Depression similar to that of reserpine
C. R., 65, F	210/110	20	180/100	40	4	Excessive sedation
G. O., 54, F	220/120	18	220/120	40	4	
E. A., 58, F	200/120	18	200/120	40	4	Excessive sedation
H. B., 35, M	170/115	26	160/110	80	10	
D. C., 38, M	160/110	30	160/110	40	8	Intermittent abdominal cramps
I. C., 60, F	180/110	24	165/90	40	20	Sedated, relaxed
M. D., 35, F	190/130	12	190/130	40	10	Depression lasting 1 week; similar to that of reserpine
M. H., 54, F	160/110	18	160/110	40	12	Sedation
M. B., 43, F	230/130	20	190/120	140	46	Relaxed, less headache and palpitation; initially B.P. 170/100, rose later
R. L., 46, F	230/130	20	200/100	150	20	O.K. on this dose; if takes more gets sedation, cramps, and urgent bowels
Averages	201/121	20	183/110	72	18	

TABLE 2.—*BAS Combined with Other Drugs in Arterial Hypertension*

Patient, age, sex	Control period		Period on therapy without BAS				Period on same therapy + BAS			Comments
	Average B.P. mm. Hg	Duration weeks	Average B.P. mm. Hg	Drugs used			Average B.P. mm. Hg	Dose of BAS mg./day	Duration weeks	
				Name	Dose mg.	Duration weeks				
A. T., 56, F	230/130	12	230/120	Rauwiloid Veriloid	3 9	8	230/120	100	30	Initially BAS caused sedation, less headache and palpitation, and a tendency to constipation
H. K., 36, F	200/120	22	180/110	Serpasil	0.75	20	150/95	40	42	More sedation on BAS
H. J., 36, M	200/120	12	180/110	Rauwiloid Veriloid	3 9	32	180/110	40	20	BAS initially reduced blood pressure to 160/90, later no effect
E. J., 45, M	190/125	28	190/125	Ansolysen	600	16	190/125	200	12	Excessive sedation on BAS
K. H., 53, F	230/120	16	230/120	Serpasil	0.25	16	200/100	40	28	
E. H., 46, M	250/160	8	230/130	Inversine	60	18	230/130	100	16	Relaxed on BAS
J. W., 46, M	220/120	14	180/100	Ansolysen	300	54	180/100	40	12	
E. A., 60, F	200/120	16	200/120	Serpasil	0.5	52	200/120	40	12	
D. C., 51, M	230/120	20	220/120	Rauwiloid Veriloid	3 9	54	220/120	40	12	
M. S., 45, M	180/130	12	180/130	Ecolid	200	24	180/130	80	14	
V. A., 50, F	230/110	4	210/110	Veriloid Apresoline Serpasil	9 200 0.4	28	190/100	50	20	
H. B., 42, M	230/120	8	200/105	Apresoline Rauwiloid Veriloid	100 5 15	100	145/85	100	25	Feels fine; flushes easily
E. C., 54, M	220/115	4	215/110	Apresoline Rauwiloid Veriloid	100 5 15	90	185/85	100	16	Sluggish, gas, and urgency of bowels
C. C., 45, M	240/130	8	230/120	Hexamethonium Apresoline Veriloid	1000 200 4	100	210/120	100	12	Feels good
F. E., 59, M	200/115	8	180/120	Ansolysen Rescinnamine	800 1	60	165/95	100	8	Sleepy initially, not later
L. G., 50, M	240/120	8	180/100	Hexamethonium Rauwiloid Veriloid	1000 4 12	100	180/100	45	12	
J. L., 50, M	220/130	8	180/110	Rauwiloid Veriloid	4 12	80	170/100	100	10	Less nervous
R. R., 45, F	240/120	8	180/115	Rauwiloid Veriloid	4 12	70	185/115	100	25	Initially BAS decreased blood pressure to 130/90, (patient sleepy); later no effect, (patient constipated)
B. S., 45, F	230/140	10	230/130	Hexamethonium Rauwiloid Veriloid	1000 4 15	10	230/130	100	20	Feels good
J. W., 45, M	220/120	8	220/120	Rauwiloid Veriloid	4 12	8	210/100	100	8	Feels good
Averages	220/124	12	202/116			47	192/109	81	18	

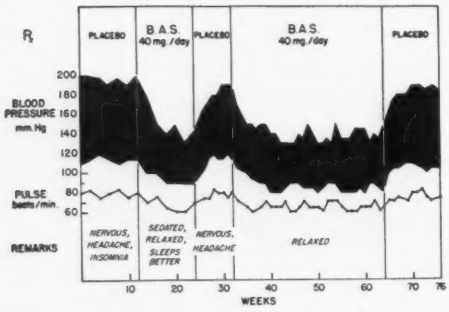

FIG. 1. Arterial pressure, pulse rate, and symptoms in a patient with essential hypertension treated alternately with placebos and BAS.

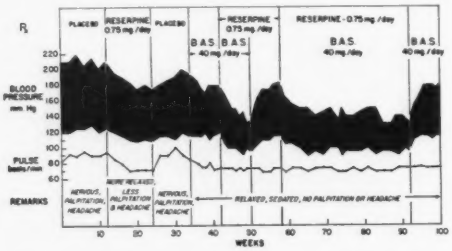

FIG. 2. Arterial pressure, pulse rate, and symptoms in a patient with arterial hypertension treated alternately with placebos, reserpine, BAS, or BAS with reserpine.

other hypotensive drugs. After an initial moderate effect the other drugs had no further hypotensive action for a full year until BAS was added. When BAS was added to the regimen the blood pressure declined nearly to normal levels.

In the 3 patients with carcinoid who were given BAS, there was a decided lessening of the symptoms of facial flushing and burning, abdominal cramps, and diarrhea of which they complained. This was described as "60 to 80 per cent relief," but it was never complete. It resembled the symptomatic benefits obtained in the same patients from oral chlorpromazine or reserpine. These benefits were less definite in the morning than in the afternoon and evening, but were considered "worthwhile" by the patients. Indeed one patient was so discouraged when, without his knowledge, he was placed on placebo and "failed" to get any further relief, that he threatened to commit suicide!

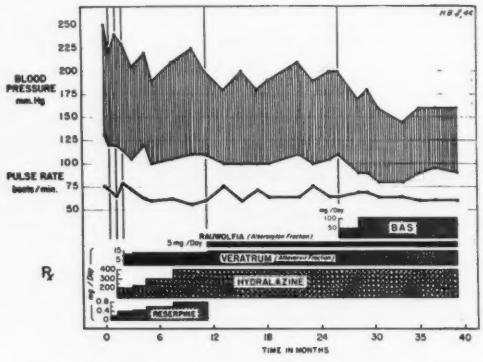

FIG. 3. Arterial pressure, pulse rate, and dosage of drugs used in a hypertensive patient over a period of 40 months. The patient never had any symptoms.

Side Effects. The side effects of BAS used in hypertensive patients resemble remarkably those of reserpine. They included sedation, or a "relaxed," "sleepy," or even "depressed" feeling. Abdominal cramps with some urgency of bowel movement were frequently noticed. There was no diarrhea but rather an urgent or explosive stool or two a day. Bradycardia also was noted by some of the patients who complained of less palpitation on the medication than off. Nasal stuffiness was noted in a number of instances but was never so severe or troublesome as that produced by rauwolfia or reserpine. BAS, like reserpine, caused a decrease in libido in a few male patients.

Of the side effects, "sedation" or "tranquilization" was the most definite and tended to limit the dosage of the drug or require its omission as patients became "too sleepy" or "depressed." In some patients, however, this sedative effect was beneficial, particularly in one who had had intractable insomnia for 15 years, which was not relieved by any medication, including barbiturates and reserpine. On 100 mg. of BAS a day this patient slept soundly from 9 p.m. to 7 a.m., and yet was fully alert during the day.

In some of the patients a type of tolerance appeared to develop on continued use of BAS. This was noted not only in the blood pressure effect, which occasionally was lost after an initial good hypotensive action, but also in the development of a state of constipation. Whether

or not this was a flaccid or a spastic type of constipation was not clear from the history of the patients. One other late, possible side effect was noted in some patients, namely a tendency to loss of appetite and weight on continued medication. This was commented upon particularly by some patients who were trying to reduce and found it definitely easier to do when taking BAS. This was in contradistinction to the increased appetite and tendency to gain weight frequently noted by patients taking reserpine.

Discussion

An antiserotonin approach to the problem of the treatment of hypertension, first suggested by Woolley and Shaw in 1952,[8] is appealing, not only because of the known "tonic" effect of serotonin on smooth muscle in general, and blood vessels in particular, but also because of the possible relationship of antiserotonin effects to the known hypotensive actions of rauwolfia and reserpine. Reserpine as an analog of yohimbine and indeed as an indole derivative could be considered to be a serotonin analog and hence possibly an antimetabolite of serotonin. Furthermore, when reserpine is given to animals it depletes the natural stores of serotonin in the brain, the platelets of the blood, and the intestinal tract.[7, 11, 12] Indeed, since the clinical action of reserpine (sedation) in such animals parallels the duration of its effect on serotonin concentrations in the brain, its action has been supposed to be dependent on its serotonin effect. This would account not only for the delay in the appearance of the clinical action of reserpine but also for the persistence of its action long after its administration has been stopped.

In our own pharmacologic studies of the hemodynamic and respiratory effects of serotonin,[4-5] we have not been able to demonstrate a clear-cut "antiserotonin" effect of reserpine given orally over long periods to patients for the treatment of hypertension. However in 1 of 5 patients retested with intravenous serotonin while taking reserpine, it was found that serotonin had a hypotensive effect during reserpine administration which it did not have during placebo control periods. A similar observation has been made in animals.[13]

Likewise in our pharmacologic studies of the antiserotonin effects of BAS it was not possible to demonstrate a clear-cut antiserotonin effect during chronic oral administration of BAS as it was after a single intravenous administration of 50 mg. BAS. However, in patients taking BAS orally for hypertension, there was a definite decrease in the subjective sensations of mental distress, and tingling and burning in the throat and face after an intravenous dose of serotonin as compared with the effects of the same dose during the control period. This subjective relief was similar to that noticed by patients with carcinoid in whom symptoms supposedly due to serotonin were decreased by BAS.

Our impression was that BAS given orally in the dosages that were tolerated for long periods in hypertensive patients (100 to 200 mg. per day) had only slight "antiserotonin" qualities, as measured by our objective methods. The only possibly significant "antiserotonin action" noted was a lessening of the symptoms produced by intravenous serotonin as already mentioned. Therefore, whether its "antiserotonin effect" had anything to do with the apparently beneficial hypotensive action of BAS observed in some of the hypertensive patients was not clear. Some other associated effect such as sedation, bradycardia, or a combination of 2 of these "side effects" rather than a direct "antiserotonin" action of BAS could have been responsible for the hypotensive results.

It is interesting that BAS is the first of the clinically useful hypotensive agents synthesized because of theoretical rather than empirical considerations. In this respect it differs from the other agents discovered by accident to be useful in hypertension, such as potassium thiocyanate, hydralazine, veratrum, and rauwolfia. However, as already suggested, it is only fair to say that the clinical usefulness of BAS, if any, may not prove to depend upon its "antiserotonin" effects. Indeed, the same may be said of reserpine. Nevertheless, an "antiserotonin approach" would seem to be a valuable one to pursue in connection with such drugs in the hope that not only better agents but a

better understanding of their actions would result. This approach would be equally valid in the field of the "tranquilizing" as of the "antihypertensive" drugs.

Summary

The benzyl analog of serotonin (BAS) alone, or in combination with other drugs, is antihypertensive in about 25 per cent of patients with essential hypertension. It also causes moderate side effects of sedation, abdominal cramps, bradycardia, nasal stuffiness, and decreased libido in this order of frequency. Whether its clinical effects in the dosage used orally in hypertensive patients are due to its antiserotonin qualities is not clear. BAS is a useful therapeutic agent in the management of some hypertensive patients.

Summario in Interlingua

Le analogo benzylic de serotonina (ABS), sol o in combination con altere drogas, es un agente antihypertensive in circa 25 pro cento del patientes con hypertension essential. Illo causa moderate effectos lateral in le sequente ordine de frequentia: Sedation, crampos abdominal, bradycardia, constipation nasal, e reduction del libidine. Il non es clar si le effectos clinic de ABS oral in le doses usate in patientes hypertensive resulta de su proprietates antiserotoninic. ABS es un agente de utilitate therapeutic in le tractamento de certe patientes hypertensive.

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Coronary Arteries in Fetuses, Infants, and Juveniles

By HENRY D. MOON, M.D.

The coronary arteries of young individuals ranging from fetuses to young adults were studied. Sclerotic lesions were not demonstrated in the coronary arteries of fetuses. In infants the early stages of arteriosclerosis were frequently present and consisted of rupture, degeneration and regeneration of the internal elastic membrane, deposition of mucopolysaccharide, and proliferation of endothelial cells and fibroblasts. These alterations were most prominent in infants of 3 to 4 months. In older individuals there was an apparent decrease in the rate of intimal fibrosis. The lesions of the coronary arteries of young individuals were identical with the early phases of arteriosclerosis in adults.

IN A previous study of the coronary arteries it was observed that many different pathologic processes participated in the development of arteriosclerosis and that these processes had an orderly sequence of evolution.[1] The earliest pathologic lesions were deposition of mucopolysaccharide in the intima, rupture and degeneration of elastic tissue, and proliferation of subendothelial fibroblasts; these were followed by regeneration of elastic tissue and formation of collagen fibers in plaques; the later stages were characterized by deposition of lipid and cholesterol, hyaline degeneration of fibrous connective tissue, calcification, intramural hemorrhage, and thrombosis. The purpose of the present study is to determine the nature and frequency of pathologic processes in the coronary arteries of young individuals.

MATERIALS AND METHODS

The hearts of 105 individuals were examined. The ages varied from fetuses of 3½ months' gestation to young adults in their early twenties. The ages and sexes are shown in table 1. In all of the individuals death had occurred suddenly, without prior clinical evidence of illness, and usually from a violent physical injury. The proximal segments of the left anterior, left circumflex, and right coronary arteries were removed and fixed in formalin, and paraffin sections were prepared. The sections were stained with hematoxylin and eosin, Weigert's elastic-tissue stain, colloidal iron-prussian blue stain for acid mucopolysaccharide,[2] and a modification of the aldehyde-fuchsin reaction[3] for elastic tissue. In many cases, frozen sections of coronary arteries were stained with oil-red O and hematoxylin and contiguous sections were stained by the procedures used for paraffin sections.

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RESULTS

Fetuses. The coronary arteries of fetuses were the only ones in which no pathologic processes were observed (fig. 1*A*). The intima consisted of a single layer of endothelial cells lying directly on the internal elastic membrane. The internal elastic membrane was a prominent band of homogeneous refractile material lying between the endothelium and smooth muscle and was essentially a continuous tube with longitudinal corrugations. The medial coat of smooth muscle cells was relatively delicate; within it very fine elastic fibrillae were present. The tunica adventitia was an indistinctly defined layer of collagenous connective tissue and some elastic fibers.

In the coronary arteries of 2 individuals, 4 to 6 weeks premature, rupture of the internal elastic membrane was observed. However, there was no reduplication or fraying of the internal elastic membrane; nor was there proliferation of endothelial cells or fibroblasts adjacent to the site of rupture of the elastic tissue.

Infants. Lesions of the proximal segments of the coronary arteries could be demonstrated in most individuals. The earliest alteration was rupture and degeneration of the internal elastic membrane. The altered segment of elastic tissue was characterized by beading, fraying, or complete disruption (fig. 2*A*, 2*B*). Small bundles of smooth muscle and fragmented elastic fibrillae were closely associated in the formation of the musculoelastic layer occupy-

TABLE 1.—*Distribution of Age and Sex of Cases*

Groups	Number		
	Male	Female	Total
Fetuses:			
3½ months to 9 months	—	—	24
Postnatal:			
0 to 2 years	36	16	52
3 to 10 years	13	5	18
11 to 22 years	5	6	11

ing the zone between the intima and media. Deposits of mucopolysaccharide were observed in these areas. In some individuals there were fibroblastic proliferation, deposition of mucopolysaccharide, and regeneration of the internal elastic membrane. Proliferation of endothelial cells overlying these areas was observed in some instances (fig. 2*E*).

In infants several months old there had been definite progression of the intimal lesions as compared with newborn infants. Diffuse intimal fibrosis extending around the entire lumen as well as localized fibrous plaques were frequently present in all of the major coronary arteries. These alterations were very pronounced in infants 3 to 4 months of age (fig. 2*C*). The intima was commonly thicker than the media. Sclerosis was more frequent and more advanced in the left anterior descending coronary artery. Mucopolysaccharide was present in varying amounts (fig. 2*F*); collagenization was minimal. In some instances the sequence of rupture and subsequent regeneration of the internal elastic membrane had apparently occurred on multiple occasions. It was not uncommon to find several layers of degenerating elastic tissue on the endothelial side of the reconstituted internal elastic membrane. Frequently very fine droplets of lipid were present in the cytoplasm of fibroblasts as well as in macrophages

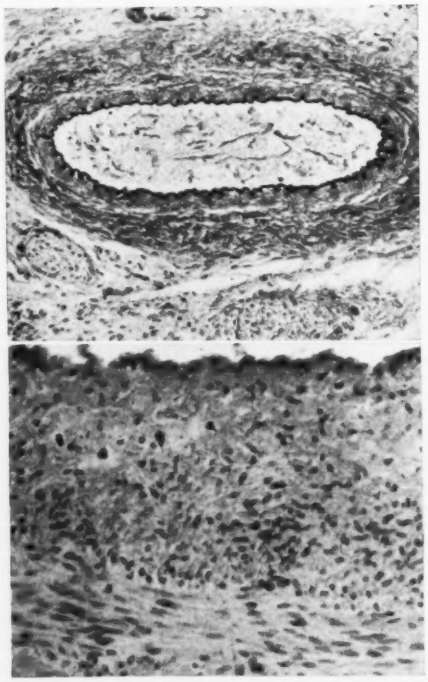

FIG. 1*A* (*Top*). Coronary artery, 5-month-old fetus. The internal elastic membrane is intact. A few delicate elastic fibrillae are present in the tunica media and adventitia. Aldehyde-fuchsin. ×55. *B* (*Bottom*). Coronary artery, 5-month-old male. There are occasionally macophages with cytoplasmic lipid in the intima. The intima is greater in thickness than the media, which lies in the lower portion of the photomicrograph. Oil-red O-hematoxylin. ×180.

FIG. 2. *A*. Coronary artery, 4-day-old female infant. There is fraying of the internal elastic membrane and increase in thickness of the intima of the lower right portion. Aldehyde-fuchsin. ×50. *B*. Higher magnification of figure 2*A* to show the area of elastic tissue undergoing alterations. Aldehyde-fuchsin. ×200. *C*. Coronary artery, 4-month-old male infant. The larger artery is eccentrically thickened by intimal reaction. The pale areas in the thickened intima represent areas of unidentified, nonlipid material. The branch to the right shows beginning alteration of the intimal layer. Weigert. ×29. *D*. Coronary artery, 2-month-old male infant. At the left there are bands of lipid in the position of the internal elastic membrane and having the configuration of this layer. The musculoelastic layer contains no demonstrable lipid. Oil-red O-hematoxylin. ×200. *E*. Coronary artery, 6-month-old male. The intima shows a plaque at the lower center. In the upper portion of the artery there is early diffuse thickening of the intima. Aldehyde-fuchsin. ×90. *F*. Higher magnification of plaque in figure 2*E*. Note rich deposit of mucopolysaccharide in the plaque. Colloidal iron. ×360. *G*. Coronary artery, 3-year-old female. There is generalized thickening of the intima. The process is accentuated adjacent to the opening of the branch. Weigert. ×21. *H*. Coronary artery, 11-year-old male. The intima is greatly thickened by fibroblastic proliferation and deposits of mucopolysaccharide. The media beneath the plaque is undergoing alterations in structure; increased amounts of mucopolysaccharide are present in the media. Colloidal iron. ×50.

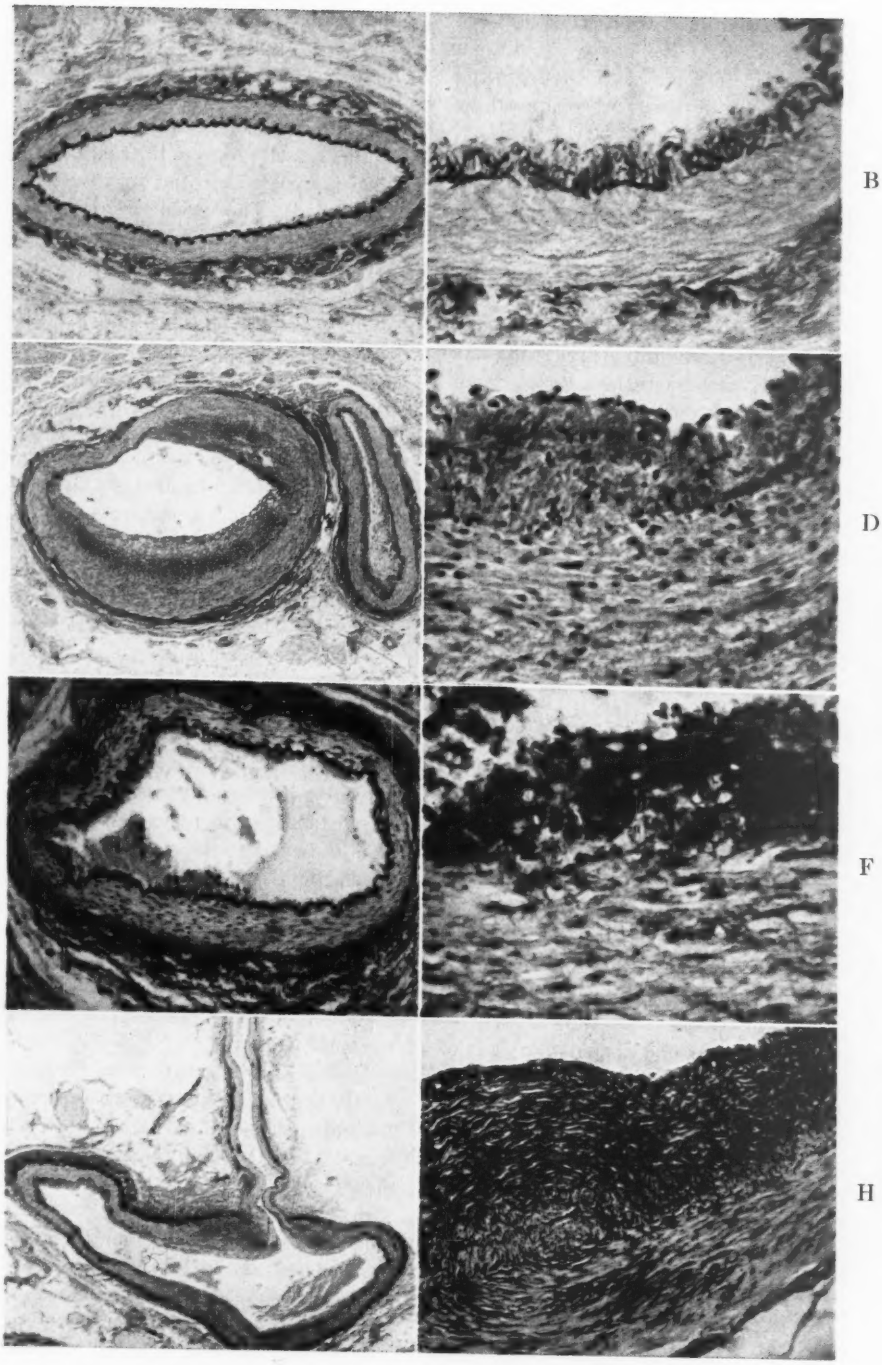

FIG. 2

(fig. 1*B*). No correlation was observed between the lipid droplets and the degree of intimal fibrosis. However, in some instances segments of degenerating elastic tissue were stained by oil-red O (fig. 2*D*).

In children 2 to 10 years of age the abnormalities noted in the intima were essentially similar to those observed in infants (fig. 2*G*). There were fibrous plaques as well as diffuse thickening of the intima. The internal elastic membrane was frequently ruptured and reduplicated, and mucopolysaccharide was present in varying amounts. Lipid droplets were occasionally present in these areas. Small amounts of collagen were present. However, in these individuals the sclerotic changes of the intima were relatively less than those in the young infants; the intima was usually thinner than the media.

In the older group, namely 10 to 22 years of age, there was evidence of continued disruption, degeneration and regeneration of elastic tissue, intimal fibrosis, and deposition of mucopolysaccharide (fig. 2*H*). Collagen was present in small amounts, and lipid was noted occasionally and in a few instances in larger amounts than seen in infants. Sex differences were observed at all ages after birth, the males exhibiting a greater degree of intimal thickening. Our observations in this regard are in essential agreement with the previous reports by Dock,[4] Fangman and Hellwig,[5] and Minkowski.[6]

Discussion

The association of lesions of the internal elastic membrane with deposition of mucopolysaccharide and subendothelial fibroblastic activity was a constant finding in the proximal segments of the coronary arteries of infants and children; this association was noted also in previous studies on the histogenesis of coronary arteriosclerosis in adults.[1] Previous studies of arteriosclerosis by many investigators[7-13] clearly demonstrate the importance of elastic tissue degeneration in the development of arteriosclerosis.

Our observations indicate that rupture and degeneration of the internal elastic membrane are the earliest demonstrable morphologic alterations. This is followed by deposition of acid mucopolysaccharide, fibroblastic proliferation, and regeneration of elastic tissue. It seems reasonable to assume that these morphologic alterations represent essentially a reaction of the vessel to an injury, e.g., intravascular tension greater than the tensile strength of the vessel wall. The proliferation of endothelial cells over early lesions may be interpreted as a part of this phenomenon. The deposition of acid mucopolysaccharide is considered to be a manifestation of fibroblastic activity. Support for this view is provided by the work of Grossfeld, Meyer, and Godman,[14] who have shown that fibroblasts in tissue culture produce hyaluronic acid. Thus, it seems reasonable to regard the early phases of the arteriosclerotic process that are already established at birth as actually a manifestation of a generalized and basic mechanism of tissue reaction to injury. This concept necessarily implicates in the development of arteriosclerosis the many factors that may influence the reaction of connective tissues to injury. The absence of the later phases of hyalinization of plaques, accumulation of large amounts of lipid, and calcification is noteworthy in young individuals. These later stages may well be a function of the aging process. The presence of lipid in some degenerating segments of elastic tissue suggests that the appearance of lipid and degeneration of elastic tissue are closely interrelated.

The absence of lesions of the internal elastic membrane and of the intima in fetuses up to the age of 8 months is noteworthy; alterations in cardiovascular function immediately preceding and following birth may, at least in part, be responsible.

It should be noted that sclerotic thickening of the intima progresses at a rapid rate for several months following birth, so that if the same rate were maintained, coronary insufficiency would occur within a matter of a few years. To some extent, the encroachment of thickened intima on the lumen is counteracted by the increase in total caliber of the vessel that occurs as a normal component of the growth process; nevertheless, there is an apparent decrease in the rate of intimal fibrosis. Although the mechanisms involved are

unknown, this decrease may be effected by a decreased rate of fibroblastic proliferation or by intermittent regression of the sclerotic process.

Summary

No lesions of the internal elastic membrane or intima were demonstrated in the coronary arteries of fetuses 3½ to 9 months of age.

The early stages of the arteriosclerotic lesion were frequently present in infants. Rupture and fragmentation of the internal elastic membrane were observed in newborn infants. This was associated with deposition of acid mucopolysaccharide, fibroblastic proliferation and, occasionally, endothelial proliferation. These processes were followed by regeneration of the internal elastic membrane. In many instances, these processes had apparently occurred repeatedly. The degree of intimal fibrosis in infants several months old was marked and indicated that this process had occurred at a rapid rate, whereas in older children and in young adults there was an apparent decrease in the rate of intimal fibrosis.

These processes of degeneration and regeneration of the internal elastic membrane, of deposition of mucopolysaccharide, and of intimal fibrosis in the coronary arteries of infants and young individuals are identical with the early nonlipid phases of arteriosclerosis in adults.

Summario in Interlingua

Nulle lesiones del interne membrana elastic o intima esseva demonstrate in le arterias coronari de fetos de inter 3½ e 9 menses de etate.

Le prime stadios de lesion arteriosclerotic esseva frequentemente presente in infantes. Ruptura e fragmentation del interne membrana elastic esseva observate in neonatos. Isto esseva associate con depositos de mucopolysaccharido acide, proliferation fibroblastic, e (in certe casos) proliferation endothelial. Iste processos esseva sequite per regeneration del interne membrana elastic. In multe casos iste processos pareva haber occurrite repetitemente. Le grado de fibrosis intimal in infantes de plure menses de etate esseva marcate e indicava que iste processo habeva occurrite rapidemente durante que in juveniles e juvene adultos le processo intimo-fibrotic pareva esser decelerate.

Iste processos de degeneration e regeneration del interne membrana elastic, de deposition de mucopolysaccharido, e di fibrosis intimal in le arterias coronari de infantes e juveniles es identic con le nonlipidic phases initial de arteriosclerosis in adultos.

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Amyloidosis of the Aorta

By H. Edward MacMahon, M.D., and Roger Coté, M.D.

A review of the literature would suggest that amyloid deposition into the intima of the aorta is an unusual finding. An opportunity to study this condition in a patient with primary amyloidosis is the basis for this report. The suggestion is made that factors responsible for this may involve mechanisms similar to those that participate in the pathogenesis of atherosclerosis.

IT IS well over a hundred years since Budd[1] in 1845 first used the expression "waxy liver" to introduce to medicine the condition now known as amyloidosis. Virchow[2] in 1858 called this waxy material amyloid. He did this on the basis of some earlier work by Meckel,[3] who in 1853 had shown that this substance has a selective affinity for iodine. Today amyloid is considered to be a particular glycoprotein that may be identified somewhat empirically with a variety of differential stains. It has been described by pathologists as a hyaline intercellular infiltrate that may occur locally or in every organ of the body. It has also been referred to as a substance that may accumulate in intercellular and connective tissue spaces in association with hyperglobulinemia. Generally speaking, cases fall into 2 groups, primary or secondary amyloidosis, depending on the presence or absence of a recognizable antecedent disease.

Textbooks of pathology, both American and foreign, seem to agree that amyloid may be found in every organ in the body, but nowhere in either the older or more recent reviews is there a description of amyloid infiltration into the intima of the aorta. Amyloidosis of large and small arteries, arterioles, capillaries, and veins is common knowledge, but its presence in the intima of the aorta must be a very unusual finding, or it has been generally overlooked, or its presence has simply been taken for granted.

The sole purpose of writing this brief report is to describe our findings in the aorta of a normotensive male patient, 55 years of age, who recently died of renal failure, the result of generalized primary amyloidosis in which the kidneys were seriously affected. Grossly the aorta was the seat of moderately severe diffuse atherosclerosis in which there was nothing to lead one to suspect the presence of amyloid. In the course of the autopsy thin sections were taken from all levels, from both atheromatous and healthy areas, and stained in the fresh state with crystal violet; to our surprise amyloid was found in varying amounts in the intima, in almost all sections, while lesser amounts were seen about the vasa vasorum in the adventitia and outer third of the media.

Grossly there may be nothing to indicate its presence in the aorta unless appropriate stains are used, and this may explain in part why it has received so little attention. In histologic sections, unless it were suspected and a number of differential stains employed, as was done in this case, it could very easily be overlooked or possibly mistaken for fibrin. In the intima it was entirely extracellular, simply lying in the ground substance in varying amounts and in varying locations. In atherosclerotic plaques it was found freely mixed with lipid in the depth of these lesions and also superficially adjacent to the endothelial lining. In areas where there was no demonstrable lipid, amyloid was seen in streaks midway between endothelium and media. In no area was there any suggestion of cellular reaction to the amyloid.

The presence of amyloid in the intima of the aorta is not just a collector's item, nor does its importance in this area depend on its functional significance, for this is probably negligible. On the contrary, its importance lies in the fact that like lipids and lipoproteins, amyloid,

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FIG. 1. Intima of the aorta, in an area of atheromatous thickening, showing a patchy accumulation of amyloid, which, in this picture, appears as a coarse, homogeneous black deposit. Crystal violet stain. × 100.

a glycoprotein, can penetrate the endothelium of the aorta, and like them can accumulate in the ground substance of the intima.

When so much attention is being focused on the etiology of arteriosclerosis, particularly in respect to the relative importance of such factors as diet, the physical characteristics of circulating lipoproteins, cholesterol levels, blood pressures, and endothelial permeability, the progressive accumulation of amyloid in precisely the same areas within the intima of the aorta as that of cholesterol may be of some interest to investigators who are concerned with the mechanisms involved in the pathogenesis of that infinitely more important disease, atherosclerosis.

SUMMARY

An instance of amyloid deposition in the intima of the aorta is described. Its possible significance is discussed.

SUMMARIO IN INTERLINGUA

Un caso de deposition de amyloide in le intima del aorta es describite. Su possibile signification es discutite.

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SYMPOSIUM ON CARDIOVASCULAR SOUND

GUEST EDITOR: VICTOR A. MCKUSICK, M.D.

I. Mechanisms

MODERATOR: HANS H. HECHT, M.D., *Salt Lake City, Utah*

VALVE MECHANICS

ROBERT F. RUSHMER, M.D., *Seattle, Wash.*

CARDIOVASCULAR sound may be divided into 2 categories,[1] namely, murmurs that result from turbulence in streams of blood flowing so rapidly that the critical Reynolds[2, 3] number is exceeded and, heart sounds that represent vibrations resulting from abrupt changes in the velocity of blood movement. Since closure of the heart valves suddenly arrests or reverses the movement of blood, normal valve function undoubtedly contributes to the production of heart sounds.

This discussion is limited to the structure and function of the atrioventricular valves, since I have not studied the semilunar valves directly. Each atrioventricular valve consists of 2 broad cusps attached at opposite sides of a large oval opening. Chordae tendineae enter the structure of the valve cusps at or near their edges to prevent eversion of the cusps when ventricular pressure is high (fig. 1). The chordae tendineae of the mitral valve insert primarily into 2 papillary muscles.[4-6] The tricuspid valve is supported by chordae tendineae from 3 papillary muscles inserting into 2 main cusps and a large intermediary cusp. Thus, the structure and function of the 2 atrioventricular valves are sufficiently similar that only the mitral valve will be considered in detail.

According to traditional concepts, an advancing gush of blood thrusts the atrioventricular valves widely open during early ventricular diastole. They are believed to be partially closed after atrial systole and clamped shut by a retrograde surge of blood at the onset of ventricular systole. These concepts have been derived primarily from observations[7, 8] and direct photography[9, 10] of valve action in *isolated* hearts, and from correlations of heart sounds with mechanical and electric events of the cardiac cycle. Cinefluorographic* observations of the motion of the mitral valve cusps in intact dogs did not confirm these concepts.[11] Such motion pictures showed the edges of the mitral valve cusps only slightly separated during ventricular filling. No abrupt movement of the valves toward the atrium was noted at the onset of ventricular systole. Indeed, the edges of the valve cusps and valve rings were observed to move toward the apex of the ventricle during systole.

The contrast between the wide valve excursions in isolated hearts and the restricted valve movements in intact animals may be explained by some recent experimental observations. One factor determining the amount of valve movement would be the degree of slack in the cusps and chordae tendineae. The amount of slack would, in turn, depend upon the size of the ventricular cavities. Roentgenographic evidence has been presented that the heart of a dog shrinks significantly when the thorax is opened, and gradually regains its normal dimensions after repair of the thoracotomy.[12] In intact dogs, the ventricles normally function at larger diastolic and systolic dimensions, so that throughout the cardiac cycle, the movements of the valves may be restrained by tension exerted by chordae tendineae. It is quite possible that normal ventricular filling is accomplished by the rush of blood through a rather narrow aperture between the valve cusps.

Similarly, there is some evidence that closure

This symposium was held in Cincinnati on October 26, 1956. The morning program, devoted to a consideration of mechanisms, appears in this issue and the afternoon program on clinical aspects will appear in next month's issue.

* The motion pictures shown in conjunction with this presentation are available for loan.

FIG. 1. Note that each papillary muscle is attached by chordae tendineae to each cusp of the mitral valve. The fibers of each chorda tendinea fan out in the substance of the cusp curtain.

of the atrioventricular valves does not result solely from a retrograde surge of blood. To produce such a displacement of blood, the dimensions of the ventricle would have to decrease as the ventricular pressure rises. Instead, the length, circumference, and internal diameter of the left ventricle all abruptly expand during the initial phase of ventricular systole.[13] These observations indicate that early contraction of papillary muscles and trabeculae carneae draw the atrioventricular valves toward the ventricular apex, closing the valves, distending the ventricular walls, and producing the initial rise in ventricular pressure. Since the chordae tendineae from each papillary muscle are inserted into each of the 2 main valve cusps, contraction of papillary muscles would tend to draw the valves together (fig. 1). Contraction of the trabeculae carneae would draw the valve ring toward the apex. Both these actions would

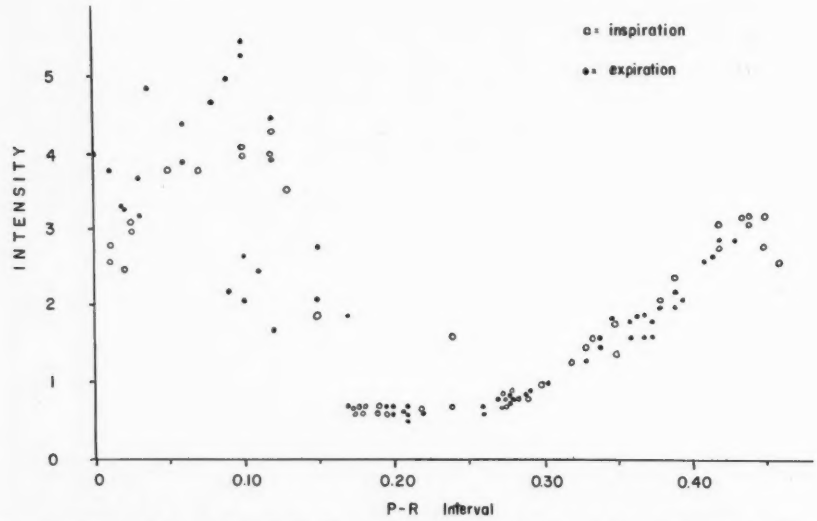

FIG. 2. (Observations of Dr. S. H. Boyer IV, Baltimore.) The relation of intensity of the first heart sound (in arbitrary units) to the duration of the P-R interval (in seconds) in a dog in which complete heart block was produced surgically by the method of Starzl and Gaertner.[37] The intensity of the first sound is presumed to be related directly to the degree of separation of the cusps at the time of contraction of the ventricle. With short P-R intervals one can infer wide separation of the cusps due to atrial systole. At longer P-R intervals (in the normal range) the cusps would appear to be close together, due probably to the "breaking of the jet" phenomenon described by Henderson and Johnson.[7] With still longer P-R intervals there has been time for the cusps to return to wider open, more neutral position. Similar curves in children have been reported.[16] ("Expiration" includes readings in both the expiratory phase proper and the phase of expiratory apnea.)

tend to elevate intraventricular pressure while distending the ventricular walls. Thus, contraction of papillary muscles may play an important role in atrioventricular valve closure when the sequence of ventricular excitation is normal.

Modifications in traditional concepts that are prompted by these studies are important in visualizing the origin of heart sounds, the changes in heart sounds owing to valvular disease, the requirements for plastic reconstruction of atrioventricular valves, and the applicability of studies of valve function in isolated or exposed hearts.

Discussion

DR. ALDO A. LUISADA (*Chicago, Ill.*): The concept that there is no remarkable ballooning of the atrioventricular valves into the atrium in ventricular systole is entirely consistent with recordings of pressure and volume events in the atria.

DR. MCKUSICK (*Baltimore, Md.*): There is interesting work demonstrating atrioventricular regurgitation in animals with atrial fibrillation.[14] The results corroborate the view[7, 8] that atrial systole normally plays a role in the closure of the atrioventricular valves. Furthermore, the data on the intensity of the first sound in relation to P-R interval are pertinent.[15, 16] Figure 2 shows data from a dog with surgically produced complete heart block.

These observations, seemingly so well accounted for by the experiments of Henderson and Johnson[7] and of Dean[8] must find other explanation if Rushmer is correct in concluding that excursion of movement of the mitral cusps is in general small. Is it not possible that with the clips applied to the margin of the cusp, Rushmer has indeed demonstrated little movement? May not, however, the main portion of the cuspal curtain be considerably more mobile? Current thinking about the valvular contribution to the heart sounds is more along the

line of tensing of the valve curtain than of actual collision of the margins of the cusps. The "inrolling"[7] of the valve in the wake of atrial systole may be accompanied by rather little motion at the margin of the cusp.

Cinematographic Studies of Normal and Abnormal Human Valves

Robert P. Glover, M.D., *Philadelphia, Pa.*

The presentation consisted of motion pictures of functioning heart valves in autopsy hearts. Ventricular function was simulated by means of a pump.[17] The mitral valve in particular was studied and mitral regurgitation was the main object of study. The effect of surgical procedures was demonstrated. Some views of the aortic valve were also provided.

Discussion

Dr. McKusick: In the specimen with considerable mitral stenosis the pictures seemed to corroborate the generally accepted idea of the origin of the mitral opening snap. The aortic leaflet of the mitral valve appeared to billow abruptly toward the ventricle at the time that would correspond to early diastole and to the time that the opening snap occurs.

It should be kept in mind that, although much valuable information pertaining to gross defects of the atrioventricular valves, either stenosis or regurgitation, can be obtained by this method, it is impossible to reproduce precisely the normal function of the atrioventricular valves. Participation of the contracting muscular ring, the role of contraction of the papillary muscles as suggested by Rushmer, and particularly the role of atrial systole are not, and cannot easily be, represented in this system. On the other hand, function of the semilunar valves can be quite precisely reproduced in a model set-up.[10]

Origin of the Heart Sounds

John J. Kelly, Jr., M.D., *Brooklyn, N. Y.*

Shortly after Laennec introduced the art of auscultation, authorities were in general agreement that the second heart sound results from the sudden tensing of the semilunar leaflets as these valves close at the end of systole. No such agreement was met in explaining the origin of the first sound. Two leading opinions have resulted; one ascribes the sound to the tensing of the atrioventricular valves and their chordae tendineae, and the other felt that the vibration of the contracting ventricular muscle mass dominates the first sound.

Phonocardiographers usually describe 4 components of the first heart sound. The first element, which is found in normal subjects, is composed of low-pitched, faint, in fact usually inaudible vibrations. The second element, which is composed of audible higher frequency oscillations, begins from 0.02 to 0.06 second after the QRS in normal subjects. This component dominates the first sound at the apex. The third element occurs from 0.07 to 0.12 second after the Q wave. This component is louder at the base of the heart over the great vessels than at the apex. It occurs with the beginning of ejection in the aorta and pulmonary arteries. When the vessels are dilated this element may be very loud as described in a "systolic click." The "fourth element" of the phonocardiographers is composed of inaudible low-frequency vibrations.

The mode of production of the second element of the first heart sound has been controversial. Because it occurs in normal subjects synchronous with the beginning of ventricular contraction, it was thought to result from muscular vibrations. Earlier experiments of Dock[18] demonstrated the disappearance of the heart sounds of an exposed dog heart when venous inflow was halted. Phonocardiographic studies relating the intensity of the first heart sound to the P-R interval implied that the first sound is caused by the sudden tensing of the atrioventricular leaflets, and that its intensity is governed to a large degree by the position of these structures at the onset of ventricular contraction. These findings failed to convert the protagonists for the muscle theory.

Studies of patients with mitral stenosis have settled this problem.[19] The time between the Q wave and first rapid vibration of the first sound (Q-1 interval) varies between 0.02 and 0.06 second if patients with bundle-branch block and mitral stenosis are excluded. In individuals with mitral stenosis, the Q-1 intervals may be

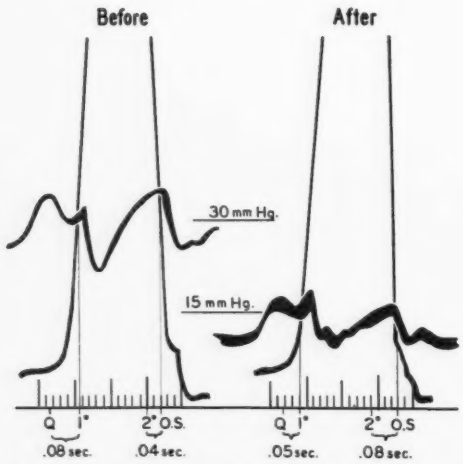

FIG. 3. Pressure recorded during operation from the left atrium and the ventricle in a patient with severe mitral stenosis. Q refers to the beginning of the QRS complex of the electrocardiogram; 1°, to the first rapid vibration of the first sound; 2°, to the second sound; O. S., to the opening snap of the mitral valve. Phonocardiograms were taken preoperatively and postoperatively when the heart rates were similar. (Courtesy of Am. J. Med.[19])

as great as 0.12 second (fig. 3). By recording pressures both in the left atrium and left ventricle in subjects undergoing mitral commissurotomy, we have found, as have others, that a wide differential in end diastolic pressure exists in these chambers when the mitral stenosis is severe. The first sound does not begin until the left ventricular pressure exceeds the elevated left atrial pressure. This may not occur for as long as 0.07 second after the onset of ventricular contraction. With enlargement of the valve orifice, atrial pressure falls and the Q-1 interval shortens (figs. 4 and 5).

This study also demonstrated that the so-called "opening snap" is indeed related to opening of the stiff mitral valve; this sound was found to occur when the left ventricular pressure fell below the left atrial pressure during relaxation of the ventricle.

Split first sounds would be expected in mitral stenosis but they are rare. In patients with mitral stenosis and prolonged Q-1 intervals, we have found no audible vibrations at the onset of right ventricular contraction as determined by cardiac catheterization.

We have attempted to evaluate the contribution of the tricuspid valve to the first sound by studying subjects with left bundle-branch block. In these individuals the right ventricle should contract first.* Onset of right ventricular contraction could be determined by the systolic deflection of an apex cardiogram or by cardiac catheterization. Splitting of the first sound was found in only 6 of 25 subjects although splitting of the second sound occurred in 20 of 25. In 5 instances a sound was found that was simultaneous with the onset of right ventricular contraction. Hence it would appear that the tricuspid contributes little to the first sound in this group. Gallops were recorded in 10 of 25 cases, 8 of the gallops occurring in presystole. The frequent association of presystolic gallop with bundle-branch block contributes to the illusion of a split first sound.†

Third heart sounds have been variously explained as due to sudden tensing of the atrioventricular valves at the end of rapid ventricular filling, to the impact of the heart against the chest wall, and to the audible vibrations of the muscular fibers when the ventricular limit of stretch is reached. This latter theory rests upon the presumption that a thick ventricular mass would respond to sudden tensing with a sound. This has been critically tested by Dock[21] who was unable to produce a sound by tensing a strip of ventricle, whereas the atrioventricular valves and strips of pericardium give off loud sounds when similarly tested.

It seems reasonable that both normal third heart sounds and gallops have a common mode of production and that a gallop is an exaggerated third heart sound.[22] We believe that they are best explained by a momentary tensing of the atrioventricular valves resulting from a reflux that follows rapid ventricular inflow.

Discussion

DR. WILLIAM LIKOFF (*Philadelphia, Pa.*): If the first heart sound is delayed, and if our ob-

* *Ed.:* However, by simultaneous right and left heart catheterizations Braunstein and Morrow[20] could demonstrate no asynchronism in left bundle-branch block.

† The vexing question of splitting of the first sound in bundle-branch block was discussed further in the afternoon program.

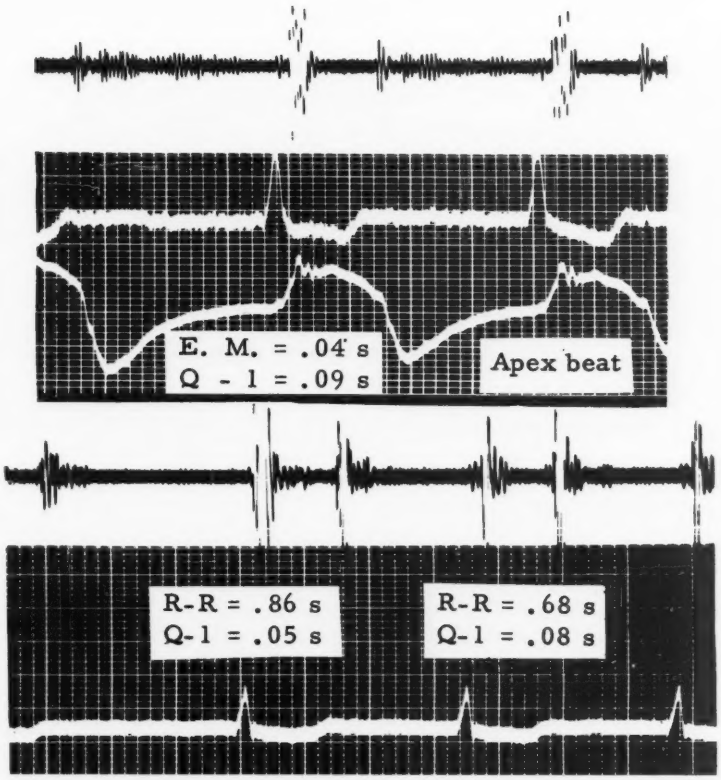

FIG. 4. *Top.* Record obtained on a middle-aged man with proved mitral stenosis. The electric-mechanical interval (E.M.) is demonstrated to be .04 second by the systolic deflection of the apex impulse. This was confirmed by direct measurement of ventricular pressure at operation. The first sound in the absence of mitral stenosis occurs at this time. In this instance the first sound begins .09 second after the beginning of the QRS. Note the deflections of the apex beat simultaneous with the first sound.

FIG. 5. *Bottom.* Trace obtained from subject with proved mitral stenosis. Atrial fibrillation with varying R-R intervals present. When the preceding diastole is long, the Q-1 is short and when diastole is short, the Q-1 lengthens. A long diastole allows better left atrial emptying and consequently a lowering of the left atrial pressure.

servation is true, that the mitral leaflet trembles and vibrates as it assumes its position of balloonment into the atrium, and if this trembling corresponds to the so-called presystolic murmur, then in fact the presystolic murmur is in systole, not diastole. I do not propose that the literature be rewritten but it is an interesting observation.

[*Ed.:* Dr. Likoff and his collaborators[23] have come to the conclusions (1) that the presystolic murmur is due to vibrations of the mitral valve in billowing toward the atrium—not to vibrations produced by the forcing of blood through the orifice with atrial systole, and (2) that the presystolic murmur is in fact systolic. These conclusions cannot be reconciled with recordings of the presystolic murmur that show its beginning well before the QRS of the electrocardiogram. With prolonged P-R intervals the "presystolic" murmur remains with the P wave and occurs even longer before the QRS. The question of whether this murmur is in actuality systolic is in part confused by the failure to distinguish electric and mechanical systole of the ventricle. It is true that the presystolic murmur continues into the first portion of electric systole

of the left ventricle. However, although it is an atriosystolic murmur, it can scarcely be considered a ventriculosystolic murmur.]

DR. LUISADA: In the past, slow vibrations initiating the first sound were considered a residuum of the effects of atrial contraction. This has been shown[24] to be incorrect, since these vibrations persist in atrial fibrillation. However, in measuring the Q-S_1 interval the first *rapid* vibrations, not these slow ones, are used.

DR. AUBREY LEATHAM (*London*): Just a plea to remember the normal ventricular asynchrony, that there are 2 ventricles and 2 sets of heart sounds and that if, as phonocardiographers, you want to split the heart sounds into 4 components, then in fact you have to split them into 8, which heaven forbid!

DR. RUSHMER: It disturbs me to hear discussions that imply the valves are vibrating alone or the chordae tendineae are vibrating alone. One must have a restoring force and a mass to produce sound. The ballooning of the valve with closure will cause overstretching and the tense valve will cause the blood to move in the opposite direction. This movement would give you the first half cycle of a vibration. But, what is going to cause the blood to move back again in the other direction and produce the multiple vibrations we record? It seems clear, to me at least, that no part of the heart is not vibrating. Basically the vibration of a system—valves, blood, wall, etc.—is involved. Consequently, when we try to isolate valves, parts of valves, or chordae, and produce sounds, I think we are off on the wrong tangent.

DR. SAMUEL A. TALBOT (*Baltimore, Md.*): I believe that in a chamber with compliant walls, there can occur local pressure fluctuations and that it is not necessary to think of the wall and the blood vibrating as a whole. Localized oscillatory mechanisms are admissible, involving local masses, local elastic properties, and local tensions. However, we must remember that no valve leaflet can move without there being considerable motion of the blood coupled with it.

In the experiments of Dock and in connection with the abrupt billowing of the mitral curtain mentioned earlier by Dr. McKusick as the probable mechanism of the mitral opening snap, it is important to keep in mind the difference between the snapping of a towel or the billowing of a sail in air, and of a valve in blood. Useful as the analogy is, the tremendously greater viscosity and density of blood, with loading of the valve cusps thereby, imposes an important difference. We should think in terms of local pressure transients—fluctuations in mean hydrostatic pressure—associated with changes in the momentum of blood.

THE GALLOP SOUNDS

Studies of the Mechanism of Production

PETER T. KUO, M.D., *Philadelphia, Pa.*

The mechanism of the gallop sound was studied previously in this laboratory with the aid of the electrokymograph.[25] A wave of rapid lateral movement of the left ventricular wall was recorded in 28 patients with severe hypertension, heart failure, and a diastolic gallop rhythm. Simultaneous phonocardiographic and electrokymographic recordings showed that the gallop sound occurred 0.01 to 0.04 second before the end of the wave of lateral movement of the ventricular wall and not after its completion. This abnormal kymographic pattern returned to normal after the patients had regained cardiac compensation and had lost the gallop sound. These observations are compatible with the view that an impact or sudden stretch of the ventricular wall is the chief cause of production of the diastolic gallop sound.*

The technics of right and left heart catheterization have made it possible to investigate further the origin of the gallop sound. In the present study, the time relationships of the gallop sound to atrial, superior vena caval, and jugular pressure pulses of the same subject were compared. Apex cardiograms were also studied in this series of 14 patients with gallop sounds. Both the piezo-electric pick-up and the Lilly capacitance manometer were employed in the recording of the apex beats.

No venous reflux wave was demonstrated in

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* *Ed.:* Brady and Taubman[26] also used electrokymography but arrived at a different conclusion.

the pressure curves taken directly from the right or the left atrium at the time the gallop sound occurred. A delay of 0.16 to 0.20 second in the transmission of the venous pulse wave from the atrium to the jugular vein was observed in these patients.

A sharp dip (inflection) following an initial upswing is often recorded in the apex beat when a piezo-electric pick-up is used. This artificial wave of apical retraction can be eliminated by the use of the amplifying system of the Lilly capacitance manometer.

Simultaneous right atrial and ventricular pressures were obtained in 4 patients with right heart failure associated with a right-sided gallop. The record showed that in all 4 patients the gallop sound occurred at the peak of the atrial "a" wave, while the right atrial pressures were 3.0 to 10.8 mm. Hg higher than those of the right ventricle.

Simultaneous recordings of the left atrial and ventricular pressures through 2 separate catheters were obtained in 10 patients with mitral insufficiency and a left-sided gallop sound. The gallop sounds were recorded in these patients when their left atrial pressures were 3.2 to 18.4 mm. Hg higher than the ventricular pressures.

It is unlikely that either the mitral or the tricuspid valves could close and vibrate while there is a sustained elevation of the atrial pressure over the ventricular pressure at the time of the gallop sound.

[*Ed.:* It is possibly important, in the design of experiments on the genesis of gallop sounds and in the reports of such experiments, to keep protodiastolic (ventricular or third sound) gallops distinct from presystolic (atrial or fourth sound) gallops. We do not know that the mechanism in the 2 is identical. Certainly the clinical setting in which each occurs is, with some overlap, distinctive: Presystolic gallops tend to accompany pulmonary and systemic arterial hypertension, aortic and pulmonary stenosis, conditions of systolic ventricular overload. Protodiastolic gallops more often are associated with myocardial failure or mitral regurgitation, conditions of diastolic ventricular overload, relative or absolute.]

Discussion

DR. FRANKLIN D. JOHNSTON (*Ann Arbor, Mich.*): I was very much interested, in Dr. Kuo's paper, to see the low-frequency vibrations that correlate with the audible gallop sounds. Many times you can see and feel gallops when they are not actually audible. The reason is obvious when you look at the low-frequency records. The vibrations are far below the major peaks in intensity or below the audible range. This simply emphasizes the importance of looking and feeling in the area of the "point of maximum impulse." Sometimes you are able to demonstrate beautifully to students a double apex impulse that goes along with a gross presystolic vibration, when you cannot hear the presystolic sound at all.

DR. LUISADA: I think that from a clinical standpoint it is important for this group to give some directives, of a semantic order, as to what is a sound and what is a murmur. A sound is very short, consisting of either 1 or 2 vibrations. When longer it should be called a murmur. If this is correct, then the heart sounds are not sounds at all but rather short murmurs; we call them sounds or tones just by habit.

DR. P. A. ONGLEY (*Boston, Mass.*): What grounds do you have for deciding to call 1 or 2 vibrations a sound and more a murmur? Should not intensity and frequency be considered in some manner?

MR. MAURICE RAPPAPORT (*Boston, Mass.*): Obviously the heart sounds, take the third sound as an example, are not pure tones. If one puts in a variable filter and gradually attenuates the low frequencies, then one will record, not the usual coarse vibrations, but a relatively high frequency sound that for obvious reasons has many vibrations. What would you call a murmur and what a sound? The number of vibrations is dependent on the characteristics of your recording system!

DR. MCKUSICK: I cannot quite see that a distinction between murmurs and sounds is possible or has any significance. The French apparently are not puzzled by this, since *bruit* is used to refer to both. The title of Calo's book is *Les bruits du coeur et des vaisseaux* (1950). The title selected for this symposium was inten-

tionally not "heart sounds and murmurs" but "cardiovascular sound."

DR. LUISADA: The French* call the heart sounds *bruits* but the murmurs *souffles*.

The clinical problem is an important one, especially when a gallop sound is present and the physician believes he is dealing with mitral stenosis. The reason for proposing 2 vibrations for a sound was purely arbitrary. If you feel differently, all right; but let's agree on something.

MR. GEORGE N. WEBB (*Baltimore, Md.*): On the basis of frequency-amplitude-time characteristics cardiovascular sound can be broken down into 3 instead of 2 categories: Firstly, impacts—transients, occurring at the time of valve closures; secondly, murmurs, which occur at constriction; and thirdly, vibrations that are musical in nature. The number of waves—1, 2, 3, or 30—is irrelevant. When we talk about sounds we should talk of what the ear interprets. The oscillogram is inadequate for displaying the characteristics by which the ear distinguishes the 3 categories. The ear is superior. The spectral phonocardiogram illustrates, inadequately as yet, the time-amplitude-frequency characteristics on the basis of which the ear makes its distinctions.

MURMURS IN RELATION TO TURBULENCE AND EDDY FORMATION IN THE CIRCULATION

D. A. MCDONALD, M.D., *London, England*

The discussion of the hydrodynamic causes of murmurs produced in the circulation must necessarily be speculative because there has been relatively little fundamental physical research into the problems of noise generation in liquids.

There are 2 main types of fluid flow regimes in steady flow conditions—laminar, or streamline, flow and turbulent flow. The conditions for the breakdown of laminar to turbulent flow were first studied in detail by Osborne Reynolds.[2] The Reynolds number is defined as the product of the velocity of flow, the diameter of the tube and the reciprocal of the kinematic viscosity* $\left(\mathrm{Re} = \frac{V \times D}{\mu}\right)$. When the Reynolds number exceeds 2,000,† laminar flow usually becomes unstable and turbulence occurs. This simple statement, however, is empirical and only applies to established steady flow in a long pipe. That is, it does not apply in any precise way to pulsatile flow or to flow conditions near the entrance of a tube (fig. 6). In the circulation of mammals the situations where murmurs are to be found all have markedly pulsatile flow and, in the case of the root of the aorta, also concern flow within the "entrance length." In a film on the nature of flow in the veins (Streamline Flow in Veins‡—D. A. McDonald and E. P. W. Helps, produced by the Wellcome Film Unit, Burroughs Wellcome) it was shown that the deviations from classical streamline flow were almost entirely due to the formation of eddies.

Laminar flow is completely silent and although it is probable that turbulent flow is accompanied by the generation of sound, it is rarely detectable on the outside of the tube in which the flow is taking place. In air streams the loudest noise generation occurs with large eddy formation.§ In view of the fact that the classical sites for murmurs—the cardiac valves and arteriovenous fistulas (the ductus arteriosus is functionally of this type)—are undoubtedly sites where many eddies are formed, it seems to be a reasonable hypothesis that the 2 phenomena are causally related.

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* *Ed.:* In fact, the French use *bruit* in both a generic and a specific sense. In the generic sense it does refer to cardiovascular sound in general. In the specific sense it refers to "the heart sounds," "souffle" (or "bruit de souffle") being used as the specific term for murmurs (or one genus of murmurs). In English, interestingly, *bruit* is used mainly to refer to murmurs, usually peripheral vascular murmurs.

* Kinematic viscosity is absolute viscosity divided by density.

† *Ed.:* Values of about 1000 are found elsewhere in the biological literature (e.g., ref. 3), merely because radius, not diameter, is used in the Reynolds formula by some workers.

‡ A copy of this film is available from the American Heart Association.

§ *Ed.:* In the original presentation "vortex-formation" was used throughout. As brought out in the discussion (see below), it may be preferable to substitute "eddy" for "vortex."

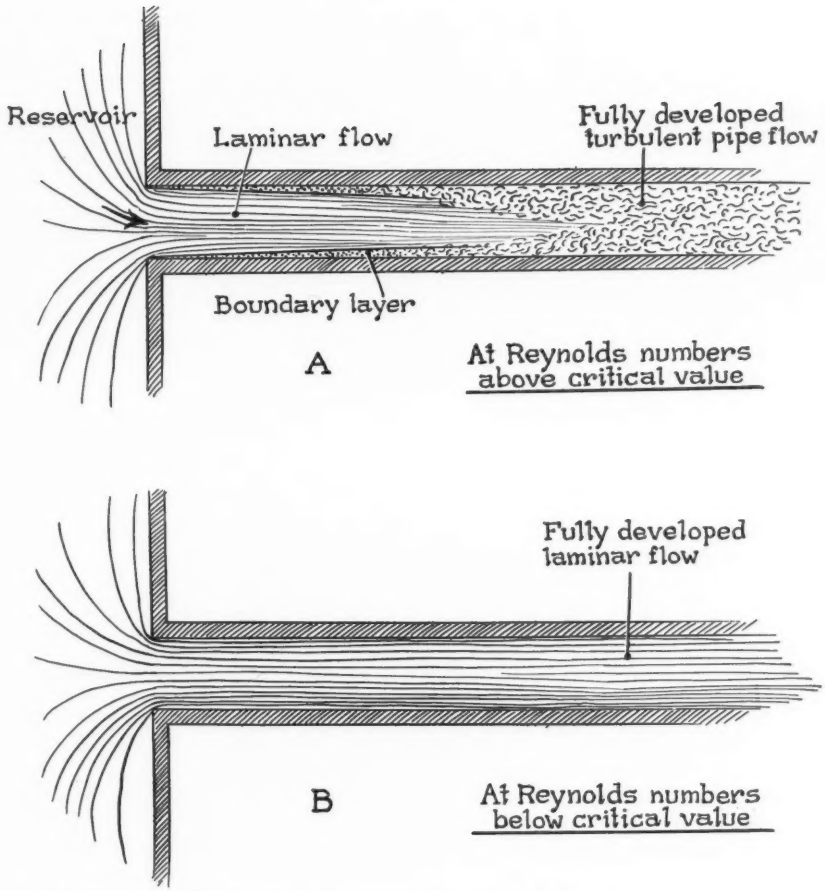

FIG. 6. The drawings illustrate the "entrance length," before the flow pattern—turbulent or laminar—is established. In the case of laminar flow, the drawing attempts to represent the parabolic velocity profile with most rapid flow at the center of the pipe.

To produce sound loud enough to be heard outside the body it is probable that some solid structure must be vibrated by the disturbed flow. The chordae tendineae of the ventricle, the valve cusps, and even the vessel walls are the structures probably involved. Dawes, Mott, and Widdicombe[27] showed, for example, that the ductus arteriosus murmur was always accompanied by a palpable vibration of the wall of the pulmonary artery. Frequency analyses of murmurs, as in McKusick's work, might be most helpful in the analysis of this problem as it is to be expected that murmurs originating in the vibration of such solid structures will have a low fundamental frequency, whereas sound arising from the fluid itself would be expected to have higher frequency components. Cavitation, the formation and collapse of gas bubbles in the circulation (fig. 7), is also a possible source of sound—probably of high frequencies.

To summarize, the search for the causation of murmurs should be directed under the following headings:

I. Sound generated within the fluid itself.
   1. Due to turbulence.
   2. Due to eddy formation.

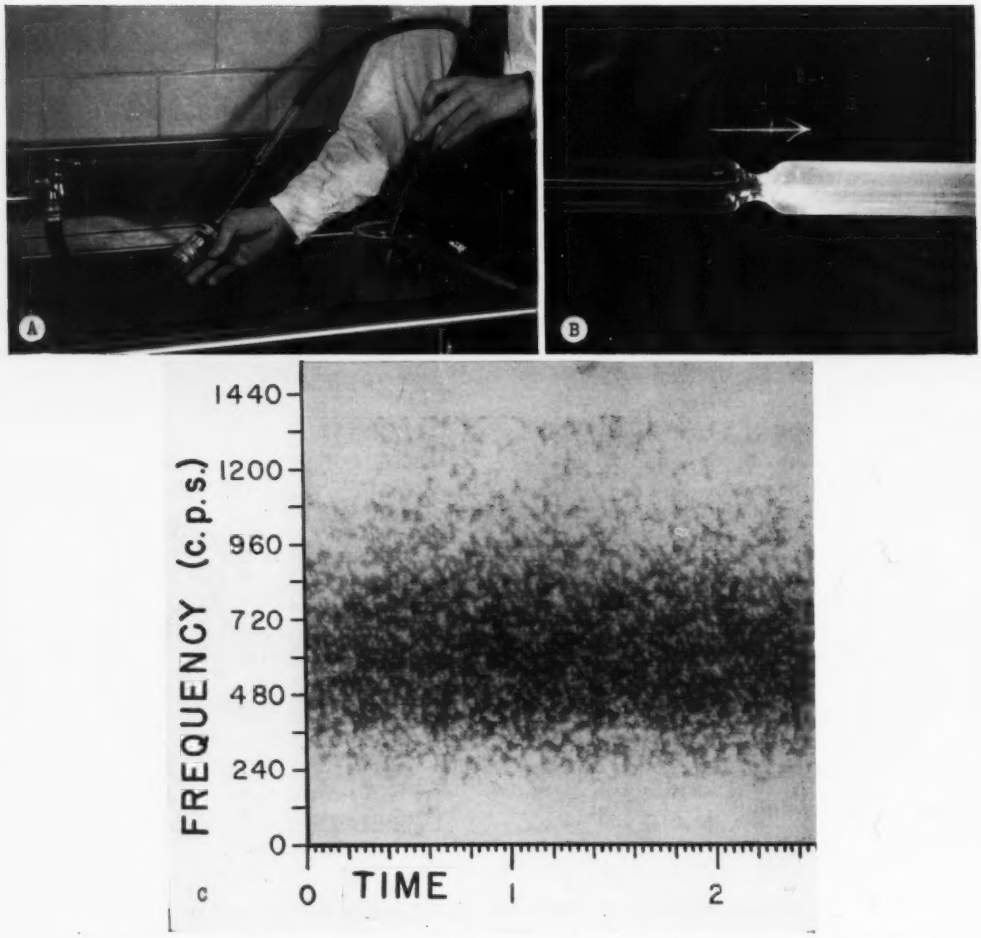

FIG. 7. When water is caused to flow through a tube with a constriction (*A*), if the velocity of flow is sufficiently high, bubbles will form at the neck (*B*) and produce a hissing noise of which the sound spectrogram is shown in *C*. The level of frequency displayed by the cavitation noise generated in this rigid-walled tube is in the upper range of that seen in murmurs. (Courtesy of Dr. McKusick.)

3. Due to cavitation—this may arise *de novo* or in association with eddies.

II. Sound generated by the vibration of solid structures.
   1. Valve margins or chordae tendineae.
   2. Jet formation impinging on a vessel wall. Ductus arteriosus and arteriovenous fistulas are the most obvious examples but jets may play a role in the root of the aorta.

III. Resonance in solid structures as a response to sound generated in the fluid. (This merely emphasizes that the separation of groups I and II is largely artificial.)

Discussion

DR. EUGENE LEPESCHKIN (*Burlington, Vt.*): I was interested in the remark of Dr. McDonald that the Reynolds number theoretically exceeds the critical value normally in the aorta; yet we know that normal flow does not produce murmurs. I wonder whether one explanation may be that it takes time for turbulence to develop.

Once a vibration develops, resonance occurs, further turbulence is facilitated, and so on. High velocity flow in the aorta may be present for too short a time for turbulence to develop.

Principles of Fluid Flow as Seen in the Jerrard-Burton Demonstration

David H. Lewis, M.D., *Philadelphia, Pa.*

The model* originally described by Jerrard and Burton[28] clearly demonstrates laminar and turbulent flow, the parabolic velocity profile of laminar flow, and the nature of eddy currents. We have used it in lectures on hemodynamics to different groups and all have appreciated the opportunity of seeing things previously only read about. A complete description of the modified device has been given by Burton[29] and need not be repeated here. It is essentially a flow tube made of plastic with straight portions, bends, and a point of constriction. The nature of the flow pattern is demonstrated by marking the axial stream with dye. Eddy currents are seen when sawdust particles are put in the water.

Its use in teaching fluid dynamics was described in the original communication and amplified by Lewis.[30] For the purposes of this symposium 2 concepts are germane. First are the factors determining the velocity of flow. It is shown both from the demonstration and from theoretical considerations that the velocity (V) at any point (y) along the radius of the tube is dependent upon the pressure drop along the tube (P_2–P_1), the radius (r), the length (l), and the viscosity of the fluid (η). The formula for this relationship is

$$V_y = (P_2 - P_1)\left(\frac{1}{4l}\right)\left(\frac{1}{\eta}\right)(r^2 - y^2)$$

In the condition where $y = r$, that is, considering the velocity at the wall of the tube, it can be seen that the velocity here is zero. In laminar flow there is a layer of fluid that coats the wall of the vessel and is stationary. The actual flow of fluid is therefore over this outermost layer and not over the wall of the vessel itself. In laminar flow, as pointed out in engineering texts on fluid dynamics, the roughness of the wall does not affect the nature of the flow so long as it remains laminar. For the physician this point is in keeping with the present concept that roughness of vessel walls and valve surfaces is not in itself sufficient to cause murmurs.

The second point to be considered is implicit in the Reynolds number. This dimensionless expression quantifies the transition from laminar to turbulent flow and for the physician indicates the conditions necessary for the genesis of murmurs. It is usually expressed as follows:

$$Re = \frac{\rho \bar{V} r}{\eta}$$

where Re is the Reynolds number, ρ the density of the fluid, $\bar{V}$ is mean linear velocity of flow, and r and η as before, radius and viscosity, respectively. There is an element of confusion here for those who see the demonstration. It is pointed out that the larger the Reynolds number the greater is the likelihood of turbulence. It seems as though turbulence should be more likely the greater the radius, and yet just the opposite is pointed out by the demonstration. The element of confusion is the concept of mean linear velocity, which is seldom used in circulatory physiology. By substituting for mean velocity the volume rate of flow ($\dot{Q}$), which is equal to the product of mean linear velocity and cross-sectional area, the confusion is dispelled. The Reynolds number then becomes

$$Re = \frac{\rho \dot{Q}}{\pi r \eta}$$

since $\dot{Q} = \bar{V}\pi r^2$.

This revised expression predicts that turbulence and the production of murmurs may occur with an increase in the volume rate of flow as in exercise, with a decrease in the radius of the vessel as in valvular stenosis, and with a decrease in viscosity as in anemia.

Discussion

Dr. McDonald: There is some precise information bearing on the influence of roughness of the wall of the tube on flow pattern. In general, for 2 flow situations with identical Reynolds

* The first part of this presentation consisted of a demonstration of the lantern-slide model of Jerrard and Burton.

number, turbulence is more likely to occur in a tube with a roughened lining than one with a smooth lining. In other words, the critical (transitional) Reynolds number is likely to be lower in a tube with rough lining.

It should be pointed out that the model you have shown does not demonstrate turbulence in the very narrow portion where velocity is greatest, but beyond it in an area where you get very large eddy formation. Heavy vortex formation due to a jet may look like turbulence.

DR. RUSHMER: Would Dr. McDonald expand on the distinction between turbulence and vortex formation?

DR. MCDONALD: In turbulence all the fluid particles are moving at random but the disturbances occur through a small latitude. In vortices one is really dealing with laminar flow that has a circular motion. Any vortex, such as a whirlpool, has a pressure drop in its center. In the whirlpool this pressure drop creates the dent in the center. The pressure drop in vortices may be related to sound generation. Actually I would prefer to use the term "eddy" rather than "vortex" in the situation under discussion.

TRANSIENTS AS A MECHANISM IN THE PRODUCTION OF HEART SOUNDS AND MURMURS*

SIMON RODBARD, M.D. *Buffalo, N. Y.*

This study,† extending over the past several years, has been based on the theses (1) that hydrodynamic factors generate discrete bursts or transients that fuse to produce the heart sounds and murmurs and (2) that if these transients could be recorded and timed, significant new information concerning cardiac function would become available.

Heart Sounds. During the early part of the first heart sound, successive transients are generated by closure of the tricuspid and mitral valves. After a brief interval, related to the period of isometric contraction, other bursts appear, representing opening of the pulmonary and aortic valves. Such bursts also generate low-frequency vibrations of great energy and long persistence that fuse, producing the usual irregular phonocardiographic trace. Vibration analyzers of the Bell type (spectral phonocardiograph) do not provide the time resolution required to separate such transients.

To separate and time the transients in heart sounds, specially designed high-pass filters were used, thereby eliminating the commonly used frequencies (below 1,000 c.p.s.). The remaining signal was amplified, recorded on magnetic tape, and displayed by means of a cathode ray oscilloscope camera, using time-expansion technics (figs. 8 and 9).

With this method, cardiac as well as arterial sounds evoked a succession of irregularly spaced spikes that were constant in timing from beat to beat. Similar transients were obtained with intracardiac microphones (fig. 10).

Murmurs. An analysis of the acoustic phenomena accompanying flow through soft-walled vessels (fig. 11) led to a similar approach to murmurs. Thus, flow at critical velocities through a soft tube repetitively raises and lowers the distending pressure acting on the wall (in accordance with the principle outlined by Bernoulli), causing recurrent closure and producing particular sequences of transient bursts.* Hydrodynamic studies show the repetition rate of closing to be a function of (1) inlet pressure head, (2) outlet head, (3) vessel diameter, and (4) stiffness of wall. The parameters of such flow, determined by appropriate model experiments, provide a basis for analysis of murmurs in terms of pressure differences across valves, as well as of the nature of the orifice or vessels through which the flow is taking place. Rapid repetition rates (high pitch) are related to higher driving heads with relatively wide orifices and increased flow. The amplitude of the transient is in general related to the pressure head driving the fluid through the opening, and to the acoustic distance of the generator of the impulse.

The principles outlined are illustrated by

* Aided by a grant from the Heart Association of Erie County, N. Y.

† See references 31–35.

* A motion picture (taken at 4,000 frames per second) of the recurrent closing and opening of the vocal cords and of elastic valves and tubes was shown. The film can be obtained from Dr. Rodbard.

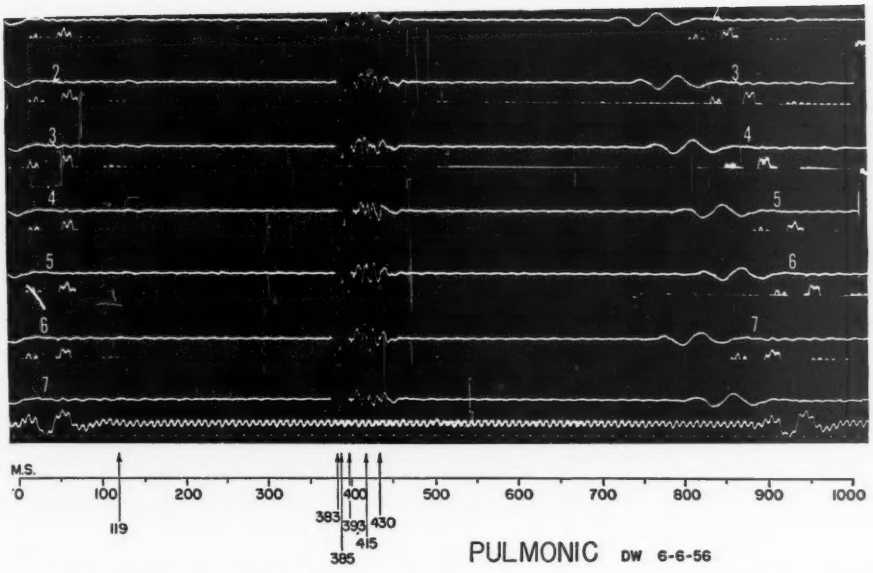

FIG. 8. Seven consecutive heart beats, recorded at the pulmonic area on a normal subject, are alined so that each QRS complex begins on the same vertical line. The first heart sound, which was relatively quiet, is represented by only a single small transient noted by the arrow at 119 milliseconds after the onset of the QRS complex. The second sound which was much louder shows a series of transients the first of which is not marked but is followed by a series that recurs consistently in each succeeding beat. In particular the transients at 400, 415, and 430 milliseconds can be clearly seen to rise above the noise level. These transients, representing very high frequencies of the order of about 5,000, may be associated with specific vibration-producing events occurring within the chest.

studies, with reference to aortic stenotic murmurs in man, in specially designed models (fig. 12). High-velocity flow produces transients as discrete repetitive openings and closings of the valves, which generate the transient spikes. The notches on the upstroke of the arterial pressure pulse wave correspond in time to the occurrence of the acoustic transients. Similar results in man have been obtained by use of a sphygmomanometer cuff to produce varying degrees of "stenosis" of the brachial artery.

The results show that high frequencies present in heart sounds and murmurs may be displayed as discrete transients. These require further investigation to determine their clinical utility.

Discussion

MR. H. KENNETH WISKIND (*Baltimore, Md.*): Dr. Rodbard's remarks are very interesting. However, I do not think we can dismiss turbulence as a murmur producer and it is otherwise of significance in cardiovascular physiology even if, as Dr. Rodbard asserts, it plays a minor role in cardiovascular sound. Therefore I would like to make a few remarks about turbulent flow.

The Critical Reynolds Number. With respect to the problem of transition from laminar to turbulent flow, the critical Reynolds number 2,000 is usually mentioned. The number 2,000 has importance only in a restricted sense. Let us consider flow from a reservoir into a pipe (fig. 6). It is important to distinguish between the pipe entrance conditions and what we call fully developed turbulent pipe flow. It is for the latter type of flow that the Reynolds number 2,000 is a reasonable criterion.

The importance of the Reynolds number lies in its use as a comparison of various flow situations, insuring that for any given situation, consistent with the basic description of the model, the dynamic state of the flow and hence its propensity for transition will be the same

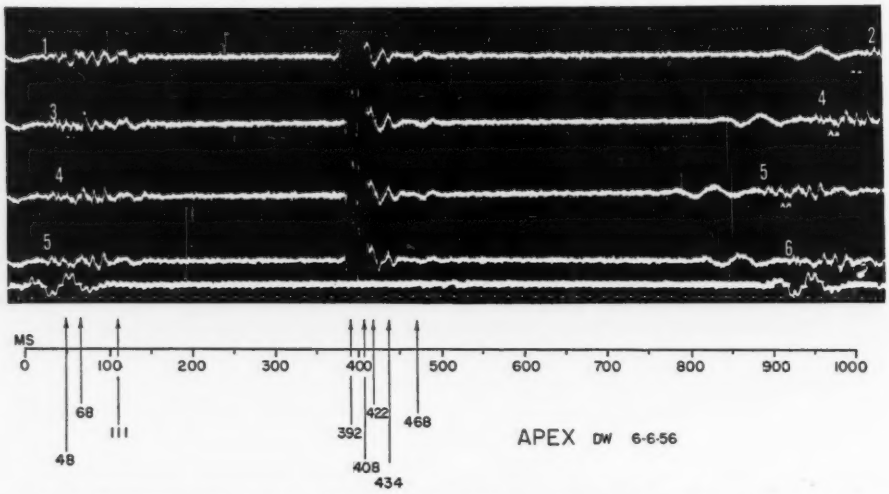

FIG. 9. Similar tracings taken at the cardiac apex on the same day show 3 transients in the first heart sound and 6 in the second.

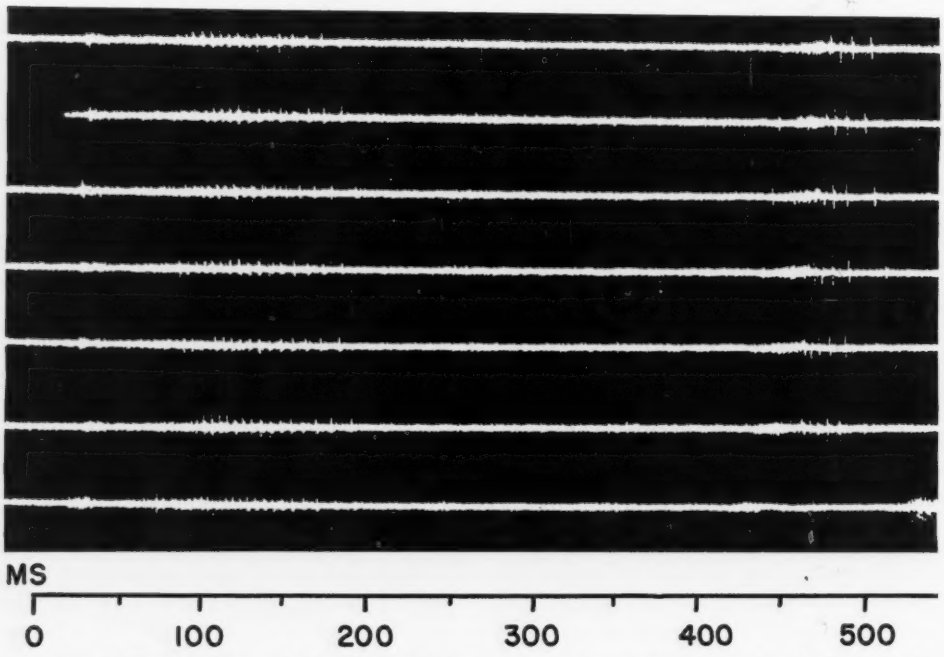

FIG. 10. Transients recorded by means of a barium titanate crystal catheter microphone inserted into the heart of a dog through the jugular vein and vena cava. Frequencies below 1,000 cycles per minute were eliminated by filter. The sounds are arranged with the scale at zero milliseconds (M.S.) placed at the onset of the Q of the electrocardiogram recorded simultaneously. The first heart sound, indicated by a series of transients, is followed by a second series of transients that increase in amplitude and then fade out. The second heart sound is not clearly determined. A presystolic sound, which was also heard at the apex, is illustrated by the several transients at the right end of each record at about 475 M.S. of the cardiac cycle.

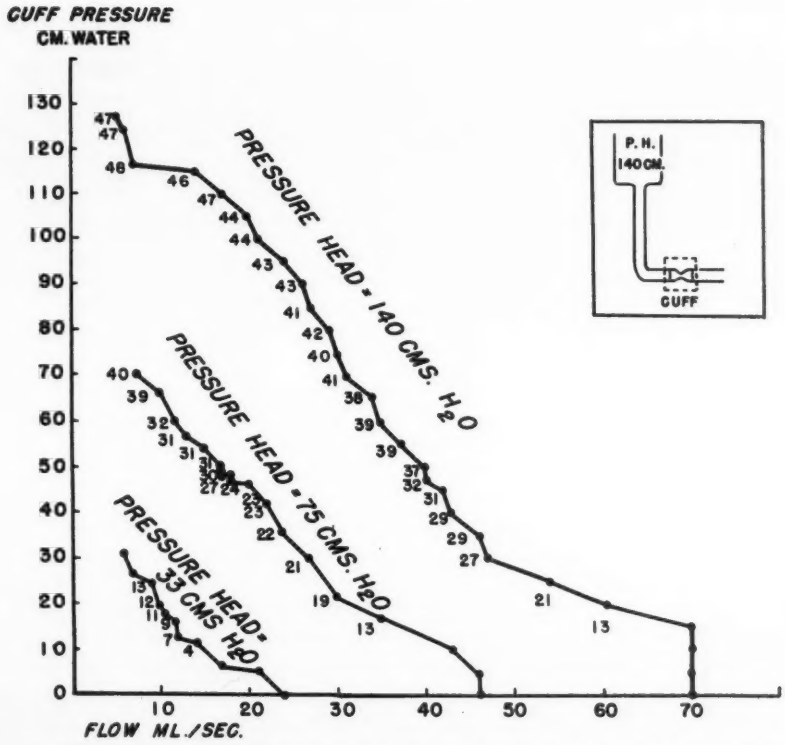

FIG. 11. Flow through a soft-walled tube using pressure heads of 140, 75, and 33 cm. of water respectively. The horizontal axis gives the delivery in milliliters per second. The vertical axis represents the degree of constriction of the tube, induced by the air pressure in the glass cuff surrounding the soft walled tube. The numbers adjacent to the 3 lines represent the repetition rate of closing and opening of the tube, as determined by stroboscope.

The upper trace shows the changes in delivery as the constriction (cuff pressure) is modified in a system with a driving head of 140 cm. of water. No effect on flow (70 ml. per second) was seen at cuff pressures from zero to 20 cm. of water. As the cuff pressure increased to 25 cm. of water, the flow fell to 60 ml. per second and the wall was observed by stroboscope to be closing repetitively 13 times each second. Increases in cuff pressure further reduced flow and increased rates of closure in a fairly consistent fashion. When cuff pressure was approximately equal to pressure head, flow fell below 5 ml. per second and closing and opening of the tube was no longer apparent. Similar data for pressure heads of 75 and 33 cm. of water are also given. The data show that the repetition rate becomes faster with either increasing pressure head or increasing degree of narrowing.

despite widely varying pipe diameters, velocities, and fluids as characterized by their kinematic viscosity. One of the consequences of this concept is the possibility of gaining a large amount of information about transition in different fluids, with a variety of pipe sizes, and over a range of velocities, from a relatively limited amount of experimentation.

The significant features of the model to which the critical Reynolds number of 2,000 is applicable are (1) straight pipe, (2) fully developed flow, i.e., without change in pattern along the pipe, and (3) steady, i.e., nonpulsatile, flow. These features obtain at a distance downsteram from the pipe entrance such that the entrance conditions no longer have an effect on the flow (fig. 6). In this region experimental evidence shows that if the Reynolds number is below approximately 2,000 the flow will be laminar and above 2,000, the flow will be turbulent.

In considering flow situations in which there

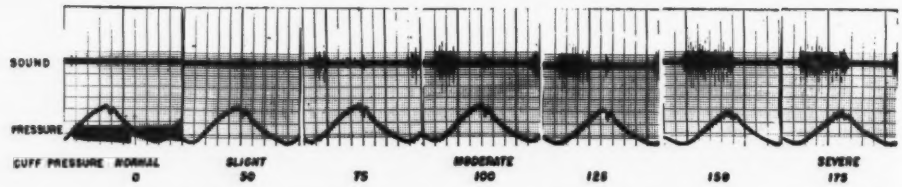

FIG. 12. Cuttings from an experiment on a circulation model showing a relation between the anacrotic incisura and the degree of constriction of a soft-walled outflow tract. The cuff pressure for each strip is given as 0, 50, 75, 100, 125, 150, and 175 cm. of water respectively. A specially designed pump raised the pressure in the "ventricle" sufficient to eject a constant stroke output in each beat; a dicrotic notch is seen near the peak of the pulse wave as the "aortic valve" closes at the end of ejection. The sound trace is given above. At cuff pressures of 0 and 50 cm. of water, the "aortic pressure" rises smoothly with ejection and no murmur is recorded. As the cuff pressure (stenosis) increases to 75 cm. of water, notches appear in the first portion of the upstroke of the "arterial pulse wave" and these are synchronous with the brief chatter of the stenosed outflow tract. With greater constriction the anacrotic notching of the "pulse wave" is more evident, the repetition rate increases and the accompanying bruit is prolonged. With severe stenosis the anacrotic incisura is even more notable, and the repetition action and bruit become holosystolic.

is a departure from the basic model, the critical (i.e., transitional) Reynolds number may very well depart greatly from 2,000. Therefore, in the consideration of the flow in the base of the aorta (which for the sake of the argument being presented can be compared to the flow at the pipe entrance in the model) it becomes higher than 2,000 because the effect of the pipe walls has not had sufficient opportunity to create fully developed pipe flow (fig. 6). Other departures from the above basic model that appear in the cardiovascular system are unsteady (i.e., pulsatile) blood flow, the arch of the aorta, the relative high elasticity of the "pipe," the state of the blood flow entering the pipe, roughness of the pipe, and obstructions in the flow.

I do not wish to imply that these departures mean that transition in blood flow cannot be predicted. I merely wish to point out that the complexities present in physiologic flows do not permit the quantitative application of results from the simplified model. However, research on the problem of transition has made significant advances in recent years and it seems reasonable that such studies applied to blood flow would be fruitful. For the present the Reynolds number can be expected to give only qualitative information.

Sound Generation from Turbulence. Turbulent flow in a free field can generate sound. This mechanism is the "demon" of the jet airplane noise problem. However, the jet of an airplane is essentially air moving at high speeds, while in the case of cardiovascular sound there is relatively low speed of movement of blood. These 2 different situations produce sounds of greatly different magnitudes. A quantitative indication of the difference can be obtained by considering the efficiency of conversion of flow energy to acoustic energy in the 2 cases. The fluid flow energy is converted into turbulent energy and then into acoustic energy and the ratio of acoustic energy to flow energy is given by $\eta \left(\frac{V}{c}\right)^5$, where V is a mean flow speed, c is the speed of sound in the medium and η is a constant of proportionality which from laboratory measurements with air jets has been determined to be approximately 10^{-4}. V/c is the Mach number, which can be high in the jets of airplanes, but since the speed of sound in blood is relatively high and the speed of blood flow relatively low, the Mach number in blood is usually low. The fact that the efficiency is proportional to the fifth power of the Mach number indicates the great sensitivity between Mach number and sound generation. Workers in underwater acoustics usually regard turbulence as a negligible factor in sound generation.

Nevertheless, there are other mechanisms by which turbulent flow can produce sound. One such situation might be turbulent flow

along an elastic panel or wall such as may exist in the aorta. In this configuration the turbulent pressure fluctuations can drive the wall which may then transmit this energy to the surface of the body where it appears as sound. However, this mechanism depends on a number of factors that require study before it can be established as a producer of cardiovascular sound.

Cavitation. It is important to think of cavitation as the appearance of bubbles, not only of the vapor phase of the liquid—water in the case of blood—but also of so-called entrained gases—in the case of blood, nitrogen, oxygen, and carbon dioxide. As they grow and collapse, bubbles of the first type, vapor bubbles, radiate noise with wide-band frequency composition (including low frequencies). Gas-entrained bubbles, on the other hand, radiate sound by excitation of their natural frequency. The compressibility of the gas in the bubble behaves as a spring. The bubble has a natural frequency of oscillation. A bubble can be excited, that is, made to oscillate around its natural size and at its natural frequency, in the process of origination, of coalescing with another bubble, and of splitting into 2 bubbles, and finally in collapsing. The natural frequency of gas-entrained bubbles is given by

$$f_0 = \frac{1}{2\pi R}\frac{3kP}{\rho}$$

where R is the radius of the tube, k is the ratio of specific heats of the gas entrained, P is the hydrostatic pressure in the liquid and ρ is the density of the liquid. Using approximate values pertinent to this discussion one arrives at $f_o = 330/R$ where R is in centimeters and f_o in cycles per second. If we consider the average radius of a bubble in the cardiovascular system to be about 1 mm., the formula yields a natural frequency of 3,300 c.p.s., a level far above that of significant components of murmurs. It follows that, if cavitation plays any role in the genesis of murmurs, vapor bubbles, not gas-entrained bubbles, are involved. The interplay between elastic wall and vibrations of wide-frequency composition—resonance, if you will —might result in murmurs with the frequency composition we in fact encounter.

It seems appropriate to make a further remark here on the origination of the cavitation bubble. The usually employed concept is that when a liquid moves rapidly enough, its static pressure may be lowered to a level below the vapor pressure and vapor bubbles appear. People concerned with this problem often either calculate or measure mean flow velocities and on this information found a judgment of the likelihood of cavitation. However, the correct conditions for the birth of a bubble need only occur in a small local region. Bubbles can appear in local areas of high velocity such as in flow around an obtuse sharp corner or in the center of a vortex, despite the fact that the mean velocity of the flow would not suggest cavitation.

Interpretation of Surface Sounds. The last comment I would like to make is on the problem of interpreting the sounds that reach the surface of the body. The body is a complex structure of which the most unusual feature from the acoustic standpoint is the fact that there is blood which is relatively incompressible within vessels that are of relatively elastic materials. As a result the transmission of the sound is very strongly dependent upon the mechanical properties of the tissues. These problems must be taken into consideration in experimental work in models and also in attempting to relate disturbances in the blood stream to sounds appearing at the surface of the body. The work of von Giercke and Oestreicher[36] emphasizes that the transmission of sound in living tissues is complex.

DR. LEPESCHKIN: The work of Dr. Rodbard links the 2 factors in the formation of murmurs: turbulence and resonance of the wall. I have found that a given amount of turbulence may not produce an audible murmur in a glass wall, but will when the flow is in a soft Tygon or polyethylene plastic tube.

DR. MCDONALD: In the formula $\eta\left(\frac{V}{c}\right)^5$, what would be the significance of defining c, not as the speed of sound in a free liquid medium, but as the speed of sound in an incompressible fluid in an elastic tube, that is in a model comparable to the aorta?

MR. WISKIND: That is an interesting point,

Dr. McDonald. The elasticity of the aorta contributes a "compressible" nature to blood flow. It causes pressure waves to travel down the aorta relatively slowly, let us say 8 M. per second, whereas the speed of pressure propagation in blood is 1,500 M. per second. Hence, a Mach number for the aorta using 8 M. per second for c might turn out to be indicative of the energy radiated from turbulent flow in the aorta. However, this remark is pure conjecture, its only significance being that, if energy is radiated from disturbances in blood flow, then the mechanical properties of surrounding tissues play an important part in determining its characteristics.

Mr. Webb: What happens, Dr. Rodbard, when you give a liquid, or chest-like, "surround" to the generator in your model?

Dr. Rodbard: There is sufficient energy for transmission of the sound to the surface of such a surround.

A word on the question of turbulence and murmurs. Homogeneous turbulence, that is, the variety produced when the critical Reynolds number is exceeded, does not produce murmurs of the coarse variety heard in aortic or pulmonic stenosis, at compressed arteries and at other sites. The sound produced by such turbulence is higher pitched than any biological sounds except the most high-pitched murmurs as in aortic insufficiency. The sounds produced by cavitation are also of a very high-pitched hissing quality and can hardly be responsible for the rumbling murmurs. I believe that good evidence supports the concept that the most common cause of murmurs will be shown to be due to repetitive closings and openings ("flitter") of the valves of the heart.

Mr. Wiskind: The frequency content of the pressure fluctuations in fully developed turbulent pipe flow is of the order of magnitude of $\frac{V}{D}$ where V is the mean velocity of flow and D is the pipe diameter. Hence, for a 150 cm. per second velocity of blood flow in a 1-cm. aorta the dominant frequency content of the turbulent fluctuations would be about 150 c.p.s. This rough rule is based on a great many experimental data in the literature. In some crude experiments in our laboratory I also found the above to be approximately true.

Editorial Summary and Comments

The details of valve mechanics continue to be shrouded in some perplexities. Rushmer's observation of minimal movement of the mitral cusps in the intact animal will require consideration in connection with the genesis of the first heart sound. Rushmer suggests that contraction of the papillary muscles may contribute to closure of the atrioventricular valves. Gradually the predominantly valvular origin of the first and second sound is attaining general acceptance. Attention is being directed to the origin of the diastolic gallop sounds. Here, too, valvular and myocardial schools are in evidence.

The discussion on mechanisms in the genesis of murmurs should serve to emphasize at least 3 points: 1. Turbulence and murmur cannot be equated in a direct manner. In our present state of knowledge the formula for the Reynolds number is useful solely as a catalog of some of the factors controlling murmur production. 2. Murmurs are produced through a complex interplay between the disturbed flow and the wall or other boundary structures. 3. Cavitation, i. e., bubble formation, as a result of local drops in pressure, should be investigated as a basis for cardiovascular sound.

Summario e Commentos Editorial in Interlingua

Le detalios del mechanica valvular continua esser obscurate per certe perplexitates. Le observation de Rushmer del minime movimento del cuspides mitral in le animal intacte va requirer consideration in connexion con le genese del prime sono cardiac. Rushmer suggere que le contraction del musculos papillar pote contribuer al clausura del valvulas atrioventricular. Le origine predominantemente valvular del prime e del secunde sono attinge gradualmente un acceptation general. Attention nunc es dirigite al origine del diastolic sonos de galopo. Etiam hic le scholas valvular e myocardiac se manifesta.

Le discussion super mechanismos in le

genese de murmures debe servir a sublinear 3 punctos al minus: 1. Turbulentia e murmure non pote esser equate de un maniera directe. In le presente stato de nostre saper le formula pro le numero Reynolds servi solmente como un catalogo de certes del factores que regula le production de murmures. 2. Murmures es producite per un complexe interaction inter le fluxo disturbate e le pariete o altere structuras limitante. 3. Cavitation, i.e., formation de bullas como resultato de local caditas in pression, debe esser investigate como un del bases de sonos cardiovascular.

ACKNOWLEDGMENT

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CLINICAL PROGRESS

Congestive Heart Failure

By EDWARD S. ORGAIN, M.D., AND EUGENE A. STEAD, JR., M.D.

THE physician, when consulted by a patient whose symptoms simulate a cardiovascular disorder, proceeds to diagnosis in systematic fashion. He determines first whether such symptoms as fatigue, dyspnea, palpitation, pain, or edema represent exaggeration of physiologic responses or whether they result from pathologic alterations of the circulation. When clinical decision favors the latter, differentiation is then made between symptoms resulting from ischemic or inflammatory changes in heart muscle, which initiate pain or disturbances in rhythm and conduction, and those related to failure of the heart as a pump, which produce the clinical picture of congestive heart failure. If symptoms point to disturbance in the ability of the heart to pump blood, he searches for objective evidence of organ dysfunction such as weakness, decreased vital capacity, pulmonary rales, increased venous pressure, engorgement of the liver, and edema. If both the history and physical findings support the diagnosis of congestive heart failure, the next step involves a clinical estimate of cardiac output. If there is considerable precordial activity, loud heart sounds, warm extremities, capillary pulse, pistol-shot sounds over the large arteries, and a low diastolic blood pressure, the cardiac output is elevated and heart failure has occurred in a setting of unusual demand for blood. Thyrotoxicosis, nutritional deficiency, anemia, patent ductus arteriosus, arteriovenous fistula, cirrhosis of the liver, and extensive Paget's disease of bone must be evaluated.

If the resting circulation is decreased, he considers first the common and then the rare types of heart disease that depress myocardial function. He attempts to establish the etiology of the heart disease and the morphologic changes produced by disease because these factors will vary his choice of therapy. He looks for secondary factors, infection or infarction, that may make the primary disease more severe. He reviews the course of treatment to determine if any present difficulties are manifestations of too vigorous therapy.

This paper reviews the more striking disturbances in physiology produced by heart failure, points out the importance of an accurate etiologic and morphologic diagnosis in relation to therapy, and differentiates between disturbances resulting from heart failure and those produced by treatment.

DISTURBANCES IN PHYSIOLOGY

The physiologic disturbances in congestive heart failure have always fascinated students of clinical medicine. Knowing that the heart supplies the peripheral tissues with blood, one might expect heart failure to produce a clinical picture of dry rot comparable to that seen in arterial occlusive disease. Instead, one finds no evidence of clear-cut nutritional deficiency in the organs but a complicated picture of weakness, dyspnea, blood and water logging of various organs, and generalized edema. The clinical picture produced by the decreased pumping action of the heart is one of organ dysfunction and congestion rather than of organ death. This is possible because organs receive blood for 2 purposes: to sustain life of the organ, and to perform the special functions that are important to the economy of the entire organism. When blood supply is reduced, the life of the tissue may not be threatened, but its capacity to perform the various specialized functions whose coordination results in smooth body function may be greatly reduced. For example, the kidney will not suffer from ischemia sufficient to produce structural damage if its blood flow is reduced to one fifth of the normal level; however, there will be

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many functions that the normal kidney can perform that the kidney with the reduced blood supply cannot.

The striking effect of the decrease in blood supply on specialized organ function has caused many persons to emphasize the peripheral effects of heart failure. We have lung failure secondary to heart failure, likewise liver failure and kidney failure. The heart, the organ directly involved and producing these secondary effects, may be completely silent. When localized injury to the heart occurs from coronary artery disease, the heart hurts and the clinical picture of angina pectoris and myocardial infarction is produced; when the pumping action of the heart is interfered with, we have congestive heart failure with no dramatic symptoms pointing directly to the heart.

Regardless of the cause, all congestive heart failure is characterized by a decrease in pumping ability of one or both ventricles. Organ dysfunction results from (a) acute congestion of organs, particularly the lungs, because one ventricle delivers blood faster than the other ventricle can remove it, and (b) decreased blood supply because of the sick heart. In acute heart failure produced either by a rapid decrease in muscle strength from myocardial infarction or by a sudden increase in work load from heavy exercise, acute pulmonary congestion resulting from left ventricular failure dominates the picture. In generalized chronic heart failure diminished organ blood flow greatly influences the clinical picture. In many patients a combination of decreased organ blood flow and of ventricular imbalance is seen.

No absolute level of cardiac output can be correlated with the presence or absence of congestive failure. The heart must pump enough blood to supply properly all of the tissues of the body and this amount of blood will vary depending on the level of organ activity. In myxedema the cardiac output may fall to low levels without the development of congestive failure. Organ blood flow will be reduced but in proportion to the degree of inactivity produced by the myxedema. In hyperthyroidism skin and muscle flow are elevated and the cardiac output is above the normal level. When the output falls to a level below that required by the hyperthyroid patient, signs of heart failure develop even though the output may be higher than that of a resting subject with a normal heart. Likewise in anemia, the heart must pump more of the thin blood and its output is increased. A decrease in output below the level needed to properly supply the organs with the thin blood will result in heart failure, though the output may still exceed that of a normal subject of similar size. The administration of packed red blood cells to an anemic subject will cause the cardiac output to fall. Heart failure may disappear as the cardiac output falls because a smaller amount of normal blood can supply the needs of the body.

In the natural course of slowly progressing heart failure, symptoms develop with a cardiac output above the resting level. Dyspnea and edema commonly appear during periods of work activity and disappear when the patient can rest from Friday night to Monday morning. During the week his heart is stimulated by his increased physical activity and responds by an increase in output. The rise is less than the needs of the body and symptoms of congestive failure develop. During the weekend he is able to rest. The heart works less but manages to supply the organs with all of the blood they need and the symptoms of congestive failure disappear.

When failure develops in patients who have illnesses that cause an increased cardiac output at rest, they will have a somewhat elevated output with failure. Their outputs are high but not high enough because of heart disease. When no complicating illnesses are present, heart failure persisting at rest is associated with a fall in cardiac output. Even though there is no reason on purely physiologic grounds for distinguishing between those patients with failure who have a high cardiac output and those who have a low output, there is a definite therapeutic reason. If the condition causing the hyperactive circulation can be corrected, the heart may prove entirely adequate for a normal load.

Fatigue is one of the dominant symptoms of congestive failure. Muscular exercise causes a large increase in blood flow to muscles and an

increase in cardiac output. If the heart is unable to supply the muscles with the extra needed blood, metabolism is altered and fatigue results.

Patients with congestive heart failure become short of wind. In more advanced failure they are dyspneic at rest and have an increased ventilatory volume. In a broad sense the dyspnea of heart disease is analogous to that caused by any diffuse disease of the lung. Failure of the heart has caused lung disease. Study of the respiration shows a decreased vital capacity and a decreased volume of residual air. It takes more effort to move air in and out of the stiffened lungs, and the muscles of respiration with an impaired blood supply become fatigued.

The lungs are engorged in congestive failure for 2 reasons. 1. Sudden and dramatic failure of the left ventricle causes the lungs to be flooded with blood. The blood accumulating in the lungs is that which is passed on to the right ventricle by venomotor mechanisms capable of propelling blood to the right side of the heart. There is less blood in the systemic circulation and more in the lungs. Because of the high capillary pressure the blood leaving the lung has lost water. As it circulates through the systemic capillaries, it picks up extracellular fluid, which it loses as it circulates through the lungs. In its pure form this type of pulmonary edema occurs without weight gain. The pulmonary edema fluid is that which is normally present in the body and not an excess accumulated because of changes in renal function caused by heart failure. 2. Selective accumulation in the lungs of the water and salt retained by the kidney occurs because of increased pulmonary capillary pressure. In more chronic left ventricular failure, the pulmonary capillary pressure remains constantly elevated and the degree of pulmonary edema will vary greatly with the volume of extracellular fluid. When salt and water are ingested and not promptly excreted by the kidney, weight gain occurs. The retained fluid accumulates preferentially in areas of high capillary pressure. Under the conditions of a chronic elevation of pulmonary capillary pressure, the amount of pulmonary edema is increased by the ingestion of salt and decreased by the use of diuretics and salt restriction without changing the quantity of circulating blood in the lungs. The only requirement in the presence of an increasing extracellular volume is the persistently elevated pulmonary capillary pressure.

As pulmonary congestion becomes more severe, the resting ventilation increases. The oxygen tension of the blood is slightly lowered but not enough to affect appreciably the degree of oxygen saturation. The overbreathing causes a fall in carbon dioxide tension and a tendency to respiratory alkalosis. The increased ventilation masks the degree of lung dysfunction that is present. If the ventilatory volume is decreased by morphine or by breath-holding, oxygen saturation of arterial blood immediately falls. The lung has lost its reservoir function, which allows the maintenance of relatively normal blood gases during periods of apnea. We see this same loss of reservoir function in persons who have a reduced lung capacity because of marked obesity. Again, minor changes in breathing rhythm are associated with marked arterial oxygen unsaturation.

We have usually looked on the level of arterial oxygen saturation as a rather fixed value. This view is relatively true in subjects with a normal vital capacity, normal pulmonary mixing, and normal alveolar capillary membranes. It becomes much less true in diseased states. In cardiac patients who have replaced air space with fluid and blood, arterial oxygen saturation will vary greatly when anything decreases the increased pulmonary ventilation. In the obese patient with decreased lung capacity, a second factor is also present. Because of the extreme degree of obesity, oxygen utilization of the body at rest is high and the oxygen left in the lung during periods of decreased ventilation is removed at a fast rate.

Edema in chronic congestive heart failure is generalized and causes a gain in weight. Sodium excretion is impaired but there is relatively little difficulty in excreting water, potassium, and nonelectrolytes. The ability of the kidney to excrete hydrogen ions and ammonia remains good. No one factor accounts for the phenomenon of edema in heart failure. Both mechanical

and hormonal factors seem to be of importance. The renal blood flow is greatly reduced and the glomerular filtrate moderately reduced in chronic heart failure, regardless of the cause of the failure. When less sodium is presented to the tubules, sodium reabsorption tends to be more complete and less is excreted. Heart failure causes an increase in the excretion and presumably the production of aldosterone, which decreases the excretion of sodium. The facts that adrenalectomy may decrease the edema of heart failure, presumably without increasing glomerular filtrate, and that aldosterone-producing tumors do not cause edema in the absence of heart failure suggest that these 2 mechanisms may operate synergistically.

The increase in central venous pressure caused by heart failure seems to be dependent primarily on increased venous tone. There is not enough blood in the lungs that can be mobilized by pulmonary venous constriction to flood the peripheral venous system and cause a marked rise in venous pressure. The central venous pressure of congestive heart failure is lowered by ganglionic-blocking agents, which interrupt sympathetic vasoconstrictor impulses to the venous system.

Hydrostatic increases in venous pressure are of major importance in determining the distribution of the salt and water retained by the kidney. During the day the high hydrostatic pressure in the dependent portions of the body may compete successfully with the lungs for retained salt and water. When the patient lies down and the hydrostatic venous pressure is lowered in the extremities, fluid re-enters the blood stream and tends to be deposited in the lungs because of the high pulmonary capillary pressure; acute nocturnal attacks of pulmonary edema may then occur.

Importance of Etiologic Factors in Heart Disease

In former years, more attention was paid to the diagnosis of heart failure and less attention to the cause of the heart disease underlying the heart failure. The therapeutic schedule was the same regardless of the cause of the failure because there were fewer specific measures available to combat the principal causes of heart disease, for example, rheumatic fever, coronary arteriosclerosis, hypertension, congenital deformities, and bacterial endocarditis. A notable exception was syphilis. During the past 30 years, additions to our knowledge of basic disease mechanisms and the introduction of effective drugs (sulfonamides, antibiotics, antihypertensives, steroids), new dietary principles (restricted sodium and low fat diets), and spectacular surgical procedures for prevention and treatment of these diseases have placed a mandatory responsibility upon the physician to recognize and treat properly such disease states in order to forestall heart injury and prevent heart failure. Classic examples would include (1) prevention of acute rheumatic fever by adequate treatment of the preceding streptococcal infection and prophylaxis of recurrent rheumatic fever by penicillin; (2) control of hypertension by drugs, diet, and sympathectomy; and (3) surgical ligation of a patent ductus arteriosus. Bacterial endocarditis, uniformly fatal in past years, now may be cured in at least 70 per cent of cases by antibiotic therapy. Although no specific therapy for coronary arteriosclerosis is presently available, the utility of prolonged anticoagulant therapy and of low-fat diets may hold promise for the future.

In addition to these common etiologic types of heart disease, it is equally important to recognize some less frequent causative factors, since they may produce congestive heart failure alone, or precipitate and maintain heart failure in previously diseased hearts. Some represent reversible forms of heart disease for which specific therapy is available; for example, hyperthyroidism, myxedema, anemia, obesity, arteriovenous fistula, constrictive pericarditis, and beriberi. Of these, hyperthyroidism is most important and easily overlooked unless clinical suspicion embraces every older patient exhibiting congestive failure and atrial fibrillation, particularly when fibrillation fails to respond to adequate digitalis dosage. The presence of normal sinus rhythm during congestive failure or an essentially normal heart rate after digitalization does not exclude the diagnosis of hyperthyroidism. Prominent staring eyes,

silky moist skin, weight loss, which may be hidden by edema, enlarged thyroid, forceful heart sounds, wide pulse pressure, absence of constipation when confined to bed, and systolic sounds over great vessels represent clues to diagnosis and the need for determinations of blood cholesterol, basal metabolic rate, protein-bound iodine, or radioactive iodine uptake for confirmation. Myxedema is missed when one fails to appreciate the significance of hair loss, dry pallid skin, husky voice, pudgy facial appearance, slow mentation, macroglossia, distant heart sounds, slow pulse, and "slow return-phase tendon reflexes," particularly in older women. The presence of an active circulation, forceful heart sounds, tachycardia, increased pulse pressure and blood velocity, and hemoglobin below 8.0 Gm. per 100 ml. of blood, strongly suggest anemia as an etiologic factor. Obesity, already mentioned as a cause of heart failure, must be considered in the massively obese patient who slumbers easily and exhibits cyanosis and Cheyne-Stokes respiration at rest. Arteriovenous fistula must be carefully excluded in those patients presenting cardiac enlargement, accentuated heart sounds, wide pulse pressure, and a history of trauma, stab, gun shot or bullet wound, or even operation for ruptured intervertebral lumbar disk. When an extremity contains a fistula, the part is larger than its counterpart, the veins are prominent, and edema will be disproportionately greater. The continuous murmur, with systolic accentuation, which can be obliterated by local pressure and thus effect cardiac slowing, is diagnostic. Excision of the fistula can restore heart size to normal or near normal after years of circulatory embarrassment and marked cardiac enlargement. Constrictive pericarditis, often confused with cirrhosis of the liver because of hepatomegaly, ascites, and edema, can be easily differentiated by the diminished heart sounds, decreased pulse pressure, "paradoxical" pulse and blood pressure, and distended neck veins secondary to elevated venous pressure. In the United States beriberi heart disease is rare and most commonly associated with chronic alcoholism and overt deficiency states, such as pellagra and polyneuritis. It is characterized by an active circulation, tachycardia, wide pulse pressure, high cardiac output, and specific therapeutic response to thiamine chloride but not to digitalis. Except for thiamine chloride there are no known states of vitamin deficiency that produce heart failure, although vitamin deficiency has long been suspected as a background for heart disease of cryptogenic etiology. Heart failure in association with cirrhosis of the liver is of uncertain etiology because of the multiplicity of factors involved, including poor nutrition, interference with protein and carbohydrate metabolism, vitamin deficiency, and anemia. It must be watched for, however, in the cirrhotic individual who develops cardiac dilatation, and must be treated before pulmonary congestion and distended neck veins appear.

Heart failure resulting from acute nephritis also should be recognized as an etiologic entity because the failure reverses spontaneously as the acute process subsides. Examination of the urinary sediment for red cell casts and fat-laden renal epithelial cells will distinguish acute nephritis from other causes of heart failure in which albuminuria, cells, and casts are commonly found. Hypertension usually accompanies nephritic heart failure but the relationship is not mandatory. Toxemia of pregnancy can be appropriately treated by caloric and sodium restriction, antihypertensive drugs, and interruption of pregnancy.

Chronic cor pulmonale with right heart failure usually results from parenchymatous disease of the lung, obstruction of pulmonary blood flow, and secondary pulmonary hypertension. Dyspnea, cyanosis, polycythemia, and clubbing of the fingers and toes are common and, when failure intervenes, venous pressure elevation, liver enlargement, and edema ensue. Primary pulmonary hypertension leading to heart failure, although rare, is a distinct entity. Often forgotten is the fact that repeated small emboli can produce cor pulmonale without cough, hemoptysis, or painful pleuritic episodes. Such emboli arise from pelvic and prostatic plexuses but more frequently from leg veins, particularly when the legs are edematous during congestive failure itself. These emboli can induce, increase, or maintain heart failure

unless their existence is suspected and appropriate treatment, either anticoagulation or venous ligation, is instituted. Suspicion should be aroused when the patient already in heart failure manifests restlessness, bouts of fever, cyanosis, dyspnea, tachycardia, unresponsiveness to the anticongestive program, and disproportionate swelling of one extremity even in the absence of painful calf muscle, Homans' sign, cough, hemoptysis, or pleural pain.

Other rare and exotic forms of heart disease causing heart failure exist but the present state of medical knowledge does not permit curative treatment. Among these may be included endocardial fibroelastosis, disseminated lupus erythematosus, scleroderma, amyloidosis, and hemochromatosis. Although steroid therapy may be of benefit in lupus disease, no specific therapy remains for the other etiologic causes. The future, however, may bring new effective methods of therapy so that continued recognition may hold interest for more than medical curiosity.

The above discussion has concerned the primary and major causes of heart disease. Often unappreciated are the common secondary and precipitating factors for heart failure when decompensation is borderline or imminent. Physical activity, not strenuous but that ordinarily pursued, may induce overt failure in the patient exhibiting cardiac enlargement and gallop rhythm or mitral stenosis. Physical exertion increases the metabolic demands of the tissues upon the heart for blood and, when cardiac output becomes inadequate for tissue needs, congestive failure results. Pulmonary edema may appear abruptly during any strenuous physical exercise when left ventricular output of blood falls below the amount delivered by the pulmonary veins, or in the presence of valvular obstruction offered by mitral stenosis.

This is also true of minor respiratory infection, particularly when associated with cough. High fever, pneumonitis, or myocarditis need not be present. That active carditis is the principal underlying cause of heart failure in rheumatic children and young adults deserves continued emphasis.

A careful history often elicits the fact that patients who suffer from rheumatic or degenerative heart disease carry on well until the onset of atrial fibrillation. Heart failure slowly appears as a result of this inefficient rhythm unless the heart rate is adequately controlled by digitalis. Rapid ectopic rhythms, particularly paroxysmal atrial and ventricular tachycardia, usually cause more abrupt appearance of heart failure by compromise of the diastolic pause of heart muscle. Although the degree of mental stress and its effects upon the body cannot be accurately measured, the importance of its existence is frequently ignored. Emotional tension and anxiety, whether acute or chronic, can convert compensation to decompensation and maintain heart failure resistant to the usual forms of therapy until such stress is ameliorated or eliminated.

Following mitral valve surgery, acute metabolic changes are often observed, which have been ascribed to the trauma and stress of operation. Urinary excretion immediately falls, water and salt are retained, blood and extracellular fluid volume rise, and the hematocrit declines. Blood sodium and chloride concentrations fall to hyponatremic and hypochloremic levels, while blood potassium concentration remains normal or even rises. Marked weakness, lethargy, dyspnea, cyanosis, and edema appear and heart failure again becomes clinically evident. One feature of the syndrome would appear to be dilution in the presence of a maintained but moderate postoperative intake of fluid in the face of a low urinary output of fluid. Blood sodium concentrations, however, frequently fall below that which can be fully accounted for by the amount of fluid retention. This suggests a transfer of sodium from the extracellular to the intracellular space where it replaces potassium. Sharp restriction of fluid intake without sodium administration in the first 96 hours is the most effective method of preventing this syndrome, which, once developed, may prove refractory to treatment and may even be fatal unless water diuresis can be achieved. Mercurial diuretics are commonly ineffective, but alcohol as an inhibitor of antidiuretic hormone holds definite promise as a therapeutic agent. The underlying cause of the metabolic disturbance is thought to be

the release of antidiuretic hormone and adrenal steroid secondary to operative stress. The possible antidiuretic effect of reduction of pressure or stretch in the left atrium by commissurotomy and relief of valve obstruction must be considered, since the syndrome is rarely as severe after other forms of cardiac or thoracic surgery. However, the syndrome has been observed in typical form after exploration of the mitral valve is undertaken without performing commissurotomy.

Classic recurrent congestive failure, occurring physiologically once monthly, is presented by a few young menstruating women suffering from mitral stenosis. During the premenstrual week, fluid retention, amounting to 5 to 10 pounds of weight gain, may culminate in increasing dyspnea, edema, and cardiac asthma unless fluids and salt are sharply restricted and diuretics administered. Estrogen liberation in the premenstrual period is the presumed cause of the salt and water retention in these patients.

Symptoms of Congestive Heart Failure and those Resulting from Treatment

Difficulties frequently confront the physician in the differentiation of those symptoms resulting from heart failure per se, and those resulting from the therapeutic program. The problem basically is whether the patient has received too little or too much treatment. As a generalization it may be stated that those symptoms present before therapy can safely be attributed to heart failure itself; those symptoms appearing during treatment must be assumed to result from one or more phases of the treatment and must be carefully assessed, particularly when the manifestations of failure are receding. Refractoriness to treatment with appearance of new symptoms indicates a careful review of the entire clinical picture and the therapeutic program.

Cerebral symptoms comprising restlessness, irritability, poor concentration, depression, and varying degrees of mild delirium are common in advanced congestive heart failure as a result of reduced cardiac output, reduced cerebral blood flow, cerebral anoxia, and the resultant disturbance of cerebral metabolism. As heart function deteriorates, stupor and coma appear as terminal events. Restoration of compensation by proper treatment usually reverses most of these symptoms unless cerebral thrombosis is a complicating feature. In older patients the mere institution of a strict low-sodium diet has produced similar symptoms of irritability, personality change, and depression, which are reversed only by restoration of normal diet. Over-digitalization likewise can induce headache, depression, irritability, and personality change but these are usually accompanied by visual disturbance, gastrointestinal symptoms, or cardiac arrhythmias in various combinations. Electrolyte disturbances such as hyponatremia, hypochloremia, alkalosis, hypokalemia, acidosis, and azotemia are common underlying causes of cerebral symptoms. They result from too vigorous treatment of congestive failure, particularly in the presence of renal disease. During heart failure itself or during the recovery phase, acute psychoses may appear for the first time and prove resistant to treatment. Psychoses usually afflict the older, but the young and middle-aged groups are not immune.

Gastrointestinal symptoms represent an integral part of the symptomatology of heart failure. The reflex pathways existing between heart and stomach through the medulla allow anorexia, nausea, and vomiting to be produced by stimulation of the reflex arc at various points. Passive congestion of the abdominal viscera is the usual mechanism for gastric dysfunction in heart failure, and symptoms clear as compensation is restored and edema disappears. Central stimulation of the pathway in the medulla also results in nausea and vomiting. Acute myocardial infarction or the excessive deposition of digitalis glycoside in heart muscle stimulates the cardiac end of the reflex arc and often produces identical gastrointestinal symptoms. The recognition of digitalis-induced gastrointestinal symptoms is not usually difficult when digitalization is accomplished evenly over periods of 2 to 4 days, for a characteristic sequence of anorexia followed by nausea, then vomiting and, occasionally, diarrhea occurs. Large-dose therapy causes nausea and vomiting to appear more abruptly.

Additional clues to the existence of intoxication are the appearance of visual symptoms, scotomata or yellow vision, rhythm disturbances, and alterations in the electrocardiogram. In older patients, rigid dietary restriction of sodium often leads to anorexia and nausea and eventually to vomiting unless normal foods are restored or some compromise effected. Thirst, anorexia, and nausea also result from electrolyte abnormalities.

Because of varied underlying types and degrees of myocardial disease, patients suffering from congestive heart failure may exhibit A-V block, bundle-branch block, or any rhythm disturbance from premature beats to ventricular tachycardia. Rhythm disorders also may be produced by excessive doses of digitalis or may follow the potassium loss through excessive diuresis, which increases the heart's sensitivity to digitalis glycosides. When the total dosage of digitalis administered is known, the problem of differentiating digitalis toxicity from symptoms of heart disease is usually easy but may be difficult when the amount is unknown. When digitalis is first prescribed, the physician should give the optimum dose that produces the desired result—that of strengthening and slowing of the heart beat with production of diuresis and weight loss. These simple therapeutic effects are often disregarded and digitalis administration is carried to the point of intoxication. Premature ventricular beats generally appear first and are followed by coupling as toxicity from digitalis increases. Atrial fibrillation may result from the rapid administration of digitalis but rarely is ventricular tachycardia observed. When rhythm alterations are of digitalis origin, visual disturbances and gastrointestinal symptoms are often present in mild form and easily overlooked unless special inquiry is made. The electrocardiogram gives important diagnostic aid by exhibiting S-T depression, flattening or inversion of the T waves, shortening of the corrected Q-T interval ($Q\text{-}T_c$) below 0.40 second, and delay in A-V conduction time beyond 0.20 second. In most instances, full digitalization will shorten the $Q\text{-}T_c$ interval in both normal and abnormal electrocardiograms. The reduction in the mean $Q\text{-}T_c$ interval for a large group will average 0.04 second. The longer the Q-T interval initially, the greater is this effect of digitalis. Only rarely will a $Q\text{-}T_c$ remain beyond 0.40 second after digitalization is complete. Thus, when the $Q\text{-}T_c$ interval lies beyond 0.40 second, it is unlikely that full digitalization is present. The converse is not true; a $Q\text{-}T_c$ interval of 0.40 second or below does not necessarily mean that digitalization is present because the $Q\text{-}T_c$ interval in the normal or abnormal electrocardiogram may fall in this range before digitalis. Paroxysmal atrial tachycardia with block must always be suspected as a digitalis-induced rhythm. During normal rhythm the heart rate may rise and congestive failure increase from digitalis poisoning. Potassium chloride may abolish the premature beats or bigeminal rhythm produced by digitalis. When final differentiation between too much or too little digitalis cannot be made with certainty, it is best to discontinue digitalis and observe the patient as digitalis excretion proceeds. Premature beats that arise from heart failure per se generally are abolished as myocardial function improves under digitalis therapy. The use of intravenous acetylstrophanthidin to produce cardiac irritability as an indication of the residual amount of digitalis glycoside deposited in heart muscle is dangerous and impractical for general use.

One of the frequent and important problems in congestive heart failure centers upon the early recognition of alterations in electrolyte metabolism. Disturbances in the blood constituents—sodium, potassium, chloride, calcium, carbon dioxide, and nitrogen—can produce a variety of cerebral, gastrointestinal, and genitourinary symptoms including weakness, drowsiness, apathy, restlessness, confusion, irritability, thirst, anorexia, nausea, muscular cramps, decrease in urinary output, and refractoriness to diuretic treatment. Such alterations are more likely to occur when the course of heart failure is complicated by too vigorous treatment including rigid low-sodium diet, mercurial diuretics, nausea, vomiting, or diarrhea, the use of ammonium chloride, ion exchangers, or carbonic anhydrase inhibitors in the presence of renal disease or renal failure. Disturbances rarely occur in heart failure from

salt restriction alone unless mercurial diuretics are administered or renal disease is associated with excessive salt loss. Under these circumstances, particularly in older subjects, the blood electrolyte picture must be followed with special care.

The most common electrolyte alteration is a hypochloremic alkalosis resulting from loss of chloride in excess of sodium during vigorous mercurial diuresis. Elevation of blood nitrogen and refractoriness to diuretic therapy commonly accompany the syndrome. Serum sodium and potassium are normal. The syndrome is reversed by the administration of ammonium chloride and diuretic responsiveness is restored.

It is possible to distinguish 2 general forms of hyponatremia: one related primarily to sodium depletion, in which serum sodium and chlorides fall to low levels, urinary chlorides decrease, and blood nitrogen and hematocrit rise; and the second, a dilution form of hyponatremia, in which sodium and chloride are reduced in the presence of increased extracellular fluid volume and lowered hematocrit. The sequence of events in the edematous cardiac under treatment may be very helpful in clinical differentiation. If hyponatremia appears after good mobilization of edema fluid and copious diuresis, and is accompanied by cerebral and gastrointestinal symptoms or peripheral collapse, depletion of sodium by mercury has very likely occurred. Repetitive large parencenteses may also induce sodium depletion when sodium intake is restricted. The dilution type of hyponatremia must be suspected when the cardiac remains edematous, becomes refractory to treatment in spite of continued mercurial injections, and exhibits symptoms of weakness, anorexia, thirst, and drowsiness. Salt depletion is less common than dilution hyponatremia and tends to respond to hypertonic sodium chloride infusion. The dilution form is a serious disturbance and when fully developed is rarely reversed. Hyponatremia occurring in a patient who has not been treated vigorously is a sign of serious illness. Salt administration under these circumstances aggravates thirst and fails to overcome the hyponatremia. Water diuresis through improved myocardial and renal function is needed but difficult to achieve, and most patients succumb. Potassium depletion also may occur as a result of vigorous diuretic therapy, particularly if food intake is poor. This may cause an increased sensitivity of the myocardium and the appearance of ectopic rhythm disturbances as manifestations of digitalis intoxication produced by potassium deficiency. Cation-exchange resin will bind sodium, potassium, and calcium and when administered over prolonged periods can produce hyponatremia, hypokalemia, hypocalcemia, and acidosis. Ammonium chloride and carbonic anhydrase inhibitors (Diamox) produce acidosis, hyperchloremia and potassium loss. Such disturbances are more likely when both compounds are administered simultaneously in large doses for long periods, particularly in the presence of renal disease when the kidney can no longer compensate for changes in acid base equilibrium. The development of drowsiness, weakness, stupor, coma, hyperpnea, low plasma carbon dioxide content, and elevated serum chloride and nonprotein nitrogen should suggest the clinical picture.

ABSTRACTS

BLOOD COAGULATION AND THROMBOEMBOLISM

Mayer, G. A., and Connell, W. F.: Effect of Bishydroxycoumarin (Dicumarol) on Clotting Time of Whole Blood. J.A.M.A. **161:** 806 (June 30), 1956.

Although the prophylaxis and treatment of the thromboembolic diseases with orally given anticoagulants has materially reduced their morbidity and mortality, there is still strong opposition to the routine use of these drugs. This is partly due to current dissatisfaction with the reliability of the controls commonly employed. Standardized clotting time (method developed by the authors) and prothrombin activity were measured in 40 patients who were receiving Dicumarol in the treatment of cardiovascular diseases. Nine hemorrhagic accidents occurred during the study. With the onset of bleeding all standardized clotting time values were above 22 minutes, while the prothrombin activity values were within accepted therapeutic limits in two thirds of the cases. The time relations and correlation coefficients for clotting time and prothrombin activity showed that these tests measure different phases of blood coagulation. The standardized clotting time test must be meticulously performed but is not complicated and requires no extensive equipment, reagents, or specially trained personnel. The clotting time test was a more valuable guide in these cases in adjusting dosages in anticoagulant therapy than prothrombin activity tests.

KITCHELL

Schilling, F. J., and Kruesi, O. R.: Clinical Evaluation of Acenocoumarin, a New 4-Hydroxycoumarin Anticoagulant. Am. J. M. Sc. **231:** 558 (May), 1956.

The 4-hydroxycoumarin derivative, acenocoumarin, has been studied for its anticoagulant effect in 65 patients with thromboembolic conditions. The drug was administered once daily with control of therapy being maintained by means of plasma prothrombin time for periods averaging 27 days per patient. The average initial dose was 20 mg. except for patients with evidence of hepatic dysfunction, malnutrition, and cardiac or renal insufficiency, in whom smaller doses were given. The average maintenance dose was 4 to 6 mg. per day, ranging from 0.5 to 14 mg. daily. Five patients developed therapeutic hypoprothrombinemia between 12 and 24 hours after the initial dose. Excessive hypoprothrombinemia occurred in 3 patients which responded to vitamin K and K_1. After cessation of therapy the dilute prothrombin time approaches normal within 30 hours. There was no evidence of toxic side effects in these patients. This drug appears to be effective in small single daily oral doses, has no untoward side effects, and is safe in maintaining therapeutic anticoagulation.

SHUMAN

Stefanini, M., and Magalini, S. I.: Evaluation of the Hemostatic Properties of Synthetic Serotonin. Arch. Int. Med. **98:** 23 (July), 1956.

Repeated administration of synthetic serotonin (5-hydroxytryptamine) intravenously or intramuscularly failed to shorten the bleeding time or to correct the poor retraction of the clot in patients with thrombocytopenia. It fleetingly reduced the prolonged bleeding time in patients with vascular pseudohemophilia.

The drug failed to improve the bleeding tendency in thrombocytopenic states. Hemorrhage continued in 1 case of vascular pseudohemophilia, although the bleeding time was corrected to almost normal values by administration of the drug.

BERNSTEIN

Losner, S., and Volk, B. W.: Fibrinogen Concentration in Various Clinical Conditions. Am. J. M. Sc. **232:** 276 (Sept.), 1956.

The determination of fibrinogen is performed by calculating the differences in optical densities before and after clotting of a plasma-thromboplastin mixture. A simple linear relationship between plasma fibrinogen and the increase in optical density was shown by the increase in light transmittance at time of clotting. The procedure is termed "clot density method" and was employed in 75 patients with coronary occlusion, 8 patients with pulmonary edema, 20 patients with coronary insufficiency, 51 patients with rheumatic fever, 5 with bacteremia, 10 with diabetic and arteriosclerotic gangrene, and 8 patients with hepatic diseases. Serial determinations by the rapid "clot density" method revealed that the maximum fibrinogen level indicates the extent of myocardial damage and can be correlated with the severity of the clinical condition. In patients with coronary insufficiency, the fibrinogen levels remained normal. In rheumatic fever, the activity of the disease is well correlated with the fibrinogen level. In bacteremia, the fibrinogen level remained normal. The demarcation of a gangrenous level was indicated by an early decline of fibrinogen to normal from previous elevated levels. Obstructive jaundice was associated with elevated fibrinogen while parenchymatous jaundice revealed low levels. The authors conclude that the serial determination of fibrinogen may prove to be a useful tool in the diagnosis, prognosis, and management of the above conditions.

SHUMAN

Perkins, H. A., Osborn, J. J., Hurt, R., and Gerbode, F.: Neutralization of Heparin in Vivo with Protamine; A Simple Method of Estimating the Required Dose. J. Lab. & Clin. Med. **48:** 223 (Aug.), 1956.

Dogs connected to an artificial heart-lung machine occasionally develop a postoperative syndrome characterized by shock and the development of a bleeding tendency. Evidence has been obtained which indicates that the use of excessive amounts of protamine may be, in part, responsible for this picture. The protamine is administered to neutralize the effect of heparin, which must be used to prevent activation of the coagulation mechanism as the blood passes over foreign surfaces. Excess protamine can be harmful in at least 3 ways. It can prolong the clotting time; it can lower the platelet count; and it can send the dog into shock. Dogs whose blood has been passed through an extracorporeal pump are peculiarly susceptible to the hypotensive action of protamine.

A simple method is described that provides an estimate of the minimal amount of protamine needed to neutralize the heparin in the animal at any given time. The method involves an in vitro titration of the dog's heparinized blood with various concentrations of protamine. Preliminary observations in patients show that the method works as effectively in man as in the dog.

MAXWELL

CONGENITAL ANOMALIES

Schoenmackers, J., and Adebahr, G.: The Morphology of Cardiac Valves in Congenital Cardiovascular Disease and the Significance of Serous Endocarditis in the Genesis of this Disease. Arch. Kreislaufforsch. **23:** 193 (Dec.), 1955.

A serous endocarditis (subendothelial edema with destruction of collagen fibers) was found in 84 of 92 children without clinical heart disease; it is attributed to toxic or metabolic influences accompanying the disease responsible for death. A serous endocarditis was found in all of 162 cases of congenital cardiovascular abnormalities. Many of these abnormalities can be explained by primary serous endocarditis of a valve, which leads to stenosis of this valve due to swelling, retraction of scar tissue, and inhibition of growth by scar tissue; as a result of this stenosis, closure of normal fetal communications may be prevented. In other cases failure of closure to occur may be primary and the serous endocarditis secondary. At any rate, the importance of serous endocarditis in the genesis of congenital cardiac abnormalities is probably greater than generally recognized.

LEPESCHKIN

Pérez González, P., and Duque Sampayo, A.: Kartagener's Syndrome. Rev. españ. cardiol. **9:** 374 (Oct.), 1955.

This is a presentation of the eighty-eighth published case, showing dextrocardia with typical electrocardiographic findings, bronchiectasis, and absence of the frontal sinuses.

LEPESCHKIN

López, R. A.: The Most Frequent Variations of the Aortic Arch in the Human Fetus. Rev. españ. cardiol. **9:** 379 (Oct.), 1955.

Anatomic study of 50 newborn infants and fetuses showed separate origin of both subclavian and carotid arteries from the aortic arch in 4, common origin of the right carotid and subclavian in 22, and common origin of the latter with the left carotid in 22 cases. Persistence of the right aortic arch was found in 1 case; it is concluded that the terminal teratogenetic period is about 35 days. A retroesophageal right subclavian artery was found in 1 case; in this case it originated at the same level as the left subclavian artery.

LEPESCHKIN

Sellors, T. H.: Coarctation of the Aorta Associated with Aneurysm. Brit. J. Surg. **43:** 365 (Jan.), 1956.

The coexistence of aneurysm and coarctation of

the aorta has been recognized with increasing frequency since the introduction of surgery in the treatment of coarctation. If untreated, the majority of the aneurysms rupture sooner or later, so that it is a matter of paramount importance to remove the aneurysm or render it inactive. At the same time the coarctation should be excised and the healthy ends of aorta restored to continuity. Exceptionally, this can be achieved by end-to-end suture or by turning down the left subclavian artery into the descending aorta, but more usually the interval between the cut aortic ends requires to be bridged by a homograft. Most of the aneurysms occur below the coarctation at the point where a branch (usually an intercostal) comes off the aorta. The swelling tends to spread along this branch, resulting in extreme dilatation. An aneurysm may occasionally develop at the site of a persistent ductus arteriosus. Bacterial endocarditis is the other cause of aneurysmal formation. The vegetations tend to form just beyond the stricture, with aneurysmal formation at the site of weakening of the wall of the artery by infection. The author describes 3 cases in which the aneurysms and coarctation were excised en bloc and continuity was successfully restored by an aortic graft prepared by "deep" freezing and the "freeze-dry" method. In 2 of the cases the aneurysms were "congenital" and the third of mycotic origin. Hypotensive agents were used to advantage throughout most of operation, and in 1 case postoperatively to counteract the excessive temporary rise in blood pressure, which has been noted previously in a number of cases. Attention was given to the length of time the aorta can safely be clamped without endangering peripheral blood flow, notably renal. A bypassing technic was employed in 1 case to prevent development of too high a central pressure and provide additional peripheral flow.

MAXWELL

Caminiti, R.: The Eisenmenger Complex. Clinical Signs and Diagnostic Considerations in 14 Personal Cases. Cuore e circolaz. **40:** 34 (Feb.), 1956.

Among 350 consecutive cases of congenital heart disease, 14 were those of Eisenmenger complex. Cyanosis and dyspnea were present in 92 per cent, appearing early in 86 per cent. Squatting was present in only 14 per cent. The ether test was positive in 75 per cent. The systolic pulmonary artery pressure ranged between 50 and 150 mm. Hg and exceeded the systemic pressure in 2 cases. Right ventricular hypertrophy in the electrocardiogram was found in 11 cases, right bundle-branch block in 1 case.

LEPESCHKIN

CONGESTIVE HEART FAILURE

Tench, W. R.: The Triad of Tachycardia, Digitalis Toxicity and Mercurial-Fast Edema in Congestive Heart Failure Complicated by Pulmonary Embolism. Am. J. Med. **19:** 869 (Dec.), 1955. Abstracted, Circulation **15:** 394 (Mar.), 1957.

Seligman, H.: New Apparatus for Treatment of Pulmonary Edema. J.A.M.A. **161:** 721 (June 23), 1956.

It is well known that bloodless phlebotomy with tourniquets or blood pressure cuffs is valuable in the treatment of pulmonary edema. A new apparatus consisting of a small compact unit connected to 4 blood pressure cuffs is described. Powered by compressed carbon dioxide in a tank, depression of a lever on the unit causes 3 cuffs to be inflated simultaneously while the fourth remains empty. Turning the main valve one-quarter turn will automatically deflate another cuff and connect the unit to the cuff that had been empty. By rotating the valve every 15 minutes, treatment may be continued indefinitely and accurately with no disturbance to the patient and a minimum of nursing care.

KITCHELL

Griffith, G. C., Dimitroff, S. P., and Thorner, M. C.: Treatment of Chronic Congestive Heart Failure with Neohydrin for from 8 to 65 Months. Ann. Int. Med. **45:** 7 (July), 1956.

Neohydrin, an organic oral mercurial diuretic, was used with satisfactory results in the treatment of congestive cardiac failure resulting from various causes. The doses were adjusted to include 1 or 2 tablets per day. In combination with digitalis, a low-sodium diet, and other therapeutic measures, neohydrin was demonstrated to be effective in the maintenance of a nonedematous state in many patients during a period varying between 8 and 65 months. Patients with congestive failure, with albuminuria and elevated values of nonprotein nitrogen but without primary renal disease, showed an improvement of these abnormalities during treatment with neohydrin. The use of neohydrin in combination with other established therapeutic measures for the control of cardiac failure improved the secondary renal dysfunction during which the patient was maintained free of edema. However, primary renal disease remained a contraindication for the use of this drug.

WENDKOS

Riemer, A. D.: The Effect of Prednisone in the Treatment of Refractory Cardiac Edema. Bull. Johns Hopkins Hosp. **98:** 445 (June), 1956.

In a 47-year-old man with severe congestive heart failure on the basis of coronary artery disease, the usual diuretic measures rendered very imperfect results in that diuresis was poor and the patient remained bedridden with the necessity for administration of supplementary oxygen. The patient was given 15 mg. of prednisone daily. Thereafter, a pronounced diuresis with drop in body weight occurred with administration of the mercurial diuretic in

doses that were previously not effective. On the sixtieth day of prednisone administration the patient returned to full-time light work. He had been receiving prednisone continuously for 250 days at the time the manuscript was submitted.

McKusick

Perez-Stable, E., Anido, V., Pianelli, V., Bustamante, R., and Edlestein, J.: Evaluation of Diamox in the Treatment of Cardiac Failure. Rev. cubana cardiol. **16:** 469 (Dec.), 1955.

All patients remained in bed and were given digitalis and a controlled diet containing 30 mEq. of sodium and 70 mEq. of potassium at least 3 days previous to the test dose of Diamox. Diamox definitely increased the diuresis and sodium excretion and decreased body weight, but these effects were less than in the case of mercurial diuretics. It caused hyperchloremic acidosis and decreased the serum sodium until signs of sodium depletion occurred in 1 case, but did not cause hypopotassemia. The effects in 6 patients with congestive heart failure were similar to those in 2 patients without failure. The opposite effect of Diamox and mercurial diuretics on the serum chlorides and alkaline reserve makes it advisable to combine the 2 drugs in the treatment of edema in congestive heart failure.

Lepeschkin

CORONARY ARTERY DISEASE

Sellers, E. A., and You, R. W.: Deposition of Fat in Coronary Arteries after Exposure to Cold. Brit. M. J. **1:** 815 (April 14), 1956.

Rats fed a stock ration and kept at 1 to 3 C. for 10 to 18 months tended to develop lipidosis of the coronary vessels. Indirect measurements of blood pressure in a few animals gave elevated values. Total serum lipids and both free and bound cholesterol were significantly increased. Cold plus high-fat, high-cholesterol diets with choline for 6 weeks produced coronary lipidosis, whereas diet and cold without choline did not.

McKusick

Krause, S., and Krause, G.: Serum Glutamic Oxalacetic Aminopherase (Transaminase) Determinations. Value in the Diagnosis of Acute Myocardial Infarction in the Presence of Left Bundle-Branch Block. J.A.M.A. **161:** 144 (May 12), 1956.

In acute myocardial infarction early electrocardiograms may not show evidence of recent myocardial injury. A previous myocardial infarct may leave residual electrocardiographic scars that will neutralize changes characteristic of a fresh injury current. Recent myocardial infarction cannot be diagnosed with certainty by a single electrocardiographic tracing in the presence of left bundle-branch block. In such cases the authors use the spectrophotometric analysis of serum glutamic oxalacetic aminopherase (transaminase) activity to clarify the diagnosis. The authors report 2 patients with recent myocardial infarction in the presence of left bundle-branch block. In the first patient, early electrocardiograms were not diagnostic but the clinical impression was strongly supported by the elevated aminopherase value obtained at the time of the second tracing. In the second patient, the electrocardiographic diagnosis of recent myocardial infarction was even less obvious, but again the elevated aminopherase values supplied good evidence that myocardial injury had taken place. In this patient the aminopherase values showed a secondary rise after the initial decline. This might mean extension of the infarcted area and could be an important prognostic feature, a problem the authors are presently pursuing in their laboratory.

Kitchell

Siglin, I. S.: Prolonged Use of Arterenol for Shock Following Myocardial Infarction with Patient Survival. Arch. Int. Med. **98:** 372 (Sept.), 1956.

This case report exemplifies the excellent recovery following myocardial infarction with prolonged shock treated with levarterenol by continuous intravenous drip for 14 days along with parenteral cortisone for 7 days.

Survey of the literature has not revealed any case of shock following myocardial infarction treated with continuous levarterenol (Levophed) drip for over 8 days with patient survival. It is estimated that the mortality rate is between 80 per cent and 90 per cent in sustained hypotension following myocardial infarction. The delayed gradual onset of shock has been described as the clinical manifestation of progressive failure of the infarcted left ventricle and as almost invariably fatal. This is in contradistinction to the hypotension that may follow immediately after the onset of the infarction, in which case about 50 per cent of the patients recover spontaneously within 1 hour.

Bernstein

Rodstein, M.: The Characteristics of Nonfatal Myocardial Infarction in the Aged. Arch. Int. Med. **98:** 84 (July), 1956.

In a group of 700 ambulatory aged men and women studied over a 5-year period 51 cases of presumptive nonfatal myocardial infarction were diagnosed. This series showed a high incidence of cases without pain or any other symptoms referable to myocardial infarction and of cases without pain but with other symptoms referable to myocardial infarction. The groups with pain, without pain but with other symptoms, and without any symptoms were compared as to clinical, laboratory, and electrocardiographic findings. The atypical symptoms were attributable to congestive failure, cerebral anoxemia, and visceral congestion, in that order of frequency. The diagnosis was made correctly on clinical grounds

prior to electrocardiographic interpretation in all of the typical cases, in only 1 of the atypical cases, and in none of the silent cases. There was a high incidence of painless myocardial infarction in the aged of a relatively mild degree of clinical severity, which may be explained by the characteristics of this group with respect to coronary artery disease, cerebral arteriosclerosis, memory function, loss of the meaning of pain sensation, and the mental attitude of the aged patient toward symptoms of disease.

Routine electrocardiographic examination of the aged will uncover, in appreciable number, changes of major degree compatible with myocardial infarction that may be unsuspected clinically. Acute myocardial infarction should be suspected and sought for among the aged who show unexplained behavior changes, sudden signs of cerebral insufficiency, or unexplained abdominal complaints or who develop an abrupt fall in blood pressure with or without preceding surgical procedure.

BERNSTEIN

Lee, K. T., and Thomas, W. A.: Factors Associated with Changing Sex Ratio of Myocardial Infarction. Study with Special Reference to the Disproportionate Rise in Incidence of the Disease Among Older Women. Arch. Int. Med. **98:** 80 (July), 1956.

In a previous study of autopsied patients with acute myocardial infarction at Barnes Hospital the authors found a shift in the ratio of incidence of acute myocardial infarction in the 2 sexes. Prior to 1940 the incidence of acute myocardial infarction in this series was twice as high among men as among women, and during the period 1940–1954 the incidence was as high among women as it was among men. The most remarkable observation made was that the shift in the ratio of the incidence of acute myocardial infarction between the 2 sexes was due to a disproportionately sharp increase in the incidence of acute myocardial infarction among women over 60 years of age during the period of 1940–1954.

Among women, neither the average body weight nor the percentage whose weights exceeded the ideal weight range was significantly different in the 2 periods. When the weight of kidneys was used as a rough guide to the incidence and severity of systemic hypertension during life and a comparison made between the average weights of kidneys in the 2 periods, no significant differences were found in either sex. Diabetes mellitus cannot account for the sharp increase in the incidence of acute myocardial infarction among women, since the incidence of diabetes mellitus among women with acute myocardial infarction is similar in the 2 periods.

BERNSTEIN

Gage, A. A., Olson, K. C., and Chardack, W. M.: Experimental Coronary Thrombosis in the Dog. Description of a Method. Ann. Surg. **143:** 535 (April), 1956.

A method was described for the production of experimental coronary thrombosis in dogs. This consisted of the insertion of a wire, 0.03 inch in diameter and composed of 98 per cent magnesium and 2 per cent aluminum, into the lumen of the anterior descending branch of the left coronary artery at the level of the bifurcation. A similar piece of wire was advanced into the circumflex branch.

The method was tested in 45 dogs. Thirteen animals died within 3 days of the insertion of the wires, while 32 lived for 8 days or longer. Invariably the procedure led to thrombus formation, coronary occlusion, and eventual myocardial infarction. The authors suggested the possible application of this method to the evaluation of the various surgical procedures advocated for coronary arterial disease.

ABRAMSON

Kline, J. L., Stern, H., Bloomer, W. E., and Liebow, A. A.: The Application of an Induced Bronchial Collateral Circulation to the Coronary Arteries by Cardiopneumonopexy. I. Anatomical Observations. Am. J. Path. **32:** 663 (July–Aug), 1956.

The authors present the results of an experimental study in dogs of establishing a collateral circulation in the lung by ligation of a pulmonary artery and then applying this circulation to the heart by cardiopneumonopexy. The collateral vessels were demonstrated by making vinylite casts of the circulation at necropsy. The collateral circulations have been classified as transpleural and retrocardiac by the authors. The first is self-explanatory; the second is that circulation built up by the bronchial vessels to supply the lung after the pulmonary artery ligation has been done. The collateral circulation is well developed at 5 months after cardiopneumonopexy, but has been found to be well developed as early as 3 months after operation. This circulation does not prevent infarction after ligation of a coronary artery within 2 months of the cardiopneumonopexy. Implications of expanding this study to apply its principles to man are given.

HARVEY

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

Elster, K., and Wallner, A.: Comparative Electrocardiographic, Morphological and Histochemical Studies on Cat Hearts in Experimental Energetic-Dynamic Cardiac Insufficiency. Ztschr. Kreislaufforsch. **45:** 586 (Aug.), 1956.

In 8 of 12 cats that had received veratrine intraperitoneally, the Q-T interval, corrected for rate according to the square root formula, showed an increase, while the corrected interval from the Q wave to the second heart sound decreased. This is

a sign of energetic-dynamic cardiac insufficiency. In many cases determination of the Q-T interval became difficult because of fusion of T with U waves. The histologic myocardial changes, which ranged from edema to deformation and scattering of the mitochondria, showed a certain dependence on the degree of the electrocardiographic changes. Both were reversible in the initial phases of the veratrine effect. The myocardial potassium concentration was decreased in the irreversible phase but was found decreased as well as increased in the reversible phase.

LEPESCHKIN

Hensler, L.: Electrocardiographic Changes in Chronic Interstitial Nephritis. Ztschr. Kreislaufforsch. **45:** 577 (Aug.), 1956.

In the first phase of chronic interstitial nephritis, which is indistinguishable from focal nephritis, no characteristic electrocardiographic changes can be seen. In the first subgroup of the second phase, in which the kidney function but not serum electrolytes are affected, the electrocardiogram in 6 cases showed later appearance of the second heart sound while the Q-T interval was normal (in 1 case it was short). The T wave was low in 3 cases. In the second subgroup acidosis, hyperchloremia, low calcium, potassium, and sodium were present, and the electrocardiogram in 3 cases showed prolonged Q-T intervals with normal or late appearance of the second sound, tall wide U waves and low T waves. In the third subgroup serum potassium again became normal due to renal retention; in 5 cases the Q-T interval was prolonged, the second sound normal or late, and the T wave normal and the U waves were absent. In the third phase potassium was elevated while acidosis and hypocalcemia were still present; the electrocardiogram in 4 cases showed a long Q-T interval, a slightly late second sound, and pointed, narrow T waves without U waves. Left ventricular strain patterns did not appear, as no hypertension was present.

LEPESCHKIN

Sterz, H., and Violl, F.: Comparative Vector Studies in Bundle Branch Block. Ztschr. Kreislaufforsch. **45:** 459 (June), 1956.

In 8 cases of left, and in 1 of right bundle-branch block, the average vectors of QRS, S-T, and T were calculated from the 12 standard leads according to Grant, and from 3 additional leads according to Shillingford and Brigden. The discrepancies between the 2 methods in the frontal plane exceeded 30° in only 2 cases, while those in the horizontal plane exceeded 45° in 2 cases, where they reached 77°. The angle between QRS and T was 160–180° in all planes, and the discrepancies of the 2 methods did not exceed 15°.

LEPESCHKIN

Queckenstedt, H.: Electrocardiographic Changes in Secondary Cardiac Tumors. Ztschr. Kreislaufforsch. **45:** 447 (June), 1956.

Three cases of bronchial carcinoma, with extension into the pericardium, showed low voltage and atrial fibrillation; the 1 patient in whom fibrillation appeared very late, had a slow clinical course. In 1 patient with small melanotic metastases extending throughout the heart, the electrocardiogram was normal. In 1 patient with infiltration of bronchial carcinoma into the posterior ventricular wall, borderline deep Q waves in leads II and III, and inverted T waves in V_1 to V_5 were present, while in another patient with infiltration of sarcoma into the right ventricle, persistent elevation of the S-T segment was a sign of rapid tumor growth.

LEPESCHKIN

LeClair, J. M., and Parkin, T. W.: Paroxysmal Atrial Flutter Associated with Acute Gastroenteritis. Proc. Staff Meet., Mayo Clinic **31:** 431 (July), 1956.

A case is reported in which a single paroxysm of atrial flutter was associated with acute gastroenteritis. There was no history of organic heart disease. Electrocardiographic evidence of temporary subendocardial ischemia was seen during the paroxysm. The cardiac arrhythmia reverted spontaneously before treatment was administered. That the gastrointestinal disturbance acted on the cardiac centers through the vagus to cause the atrial flutter is a matter of speculation.

SIMON

Graziani, G.: The Ballistocardiogram in Muscular Activity. Acta. cardiol. **11:** 319 (Fasc. 4), 1956.

The authors studied in 100 normal persons the effect of a 2-step exercise test (according to Master) upon the ballistocardiogram which was recorded photoelectrically or electromagnetically using a rigid table. In 70 per cent of the cases muscular activity was found to increase the amplitude of all or some of the waves without changing the general appearance of the curve. In some cases the increase of the L wave was predominant, in others downard displacement of the diastolic waves was observed. Disappearance of small systolic and diastolic waves occurred with tachycardia produced by muscular activity. This seems to depend on the pulse rate rather than exercise, since it was also seen at rest in cases with a rapid heart rate.

PICK

Wynne, N. A., and Szekely, P.: The Electrocardiogram in Experimental Venous Air Embolism. Acta. cardiol. **11:** 339 (Fasc. 4), 1956.

Air embolism produced in anesthetized cats had the following electrocardiographic effects. In early stages there was depression of the S-T segment and inversion of the T wave, which were

reversible with recovery of the animal. In later stages complete atrioventricular block appeared, was always associated with a sharp drop in blood pressure and invariably fatal. In some experiments elevation of the S-T segment occurred following early depression, suggesting development of acute subepicardial ischemia. In right precordial leads a pattern of right heart strain was recorded. Atropinization or vagotomy had no effect on the electrocardiographic changes produced by the air embolism.

The left lateral position appeared to exert a favorable effect on the outcome of the experiments. Although the electrocardiographic changes were the same as those seen with the animal in supine position, onset of atrioventricular block was delayed and the survival period prolonged. There was also marked hyperpnea, which was never seen with the cats kept lying on the back.

PICK

Moret, P. R., Schwartz, M. L., Arbeit, S. R., Grossman, H. W., and Re, M. N.: A Phonocardiographic Study of Mitral Valvular Disease Complicated by Auricular Fibrillation. An Analysis of the Factors Responsible for Variations in the Time of Occurrences of the First Heart Sound and the Snap. Cardiologia **29:** 180 (Fasc. 3), 1956.

It has been previously reported that in mitral stenosis the presence or absence of an associated mitral or aortic regurgitation can be determined by certain phonocardiographic features. In mitral stenosis the distance of the R wave to the beginning of the first sound varies inversely with the length of the preceding cycle, while the distance of the second sound to the opening snap varies proportionately to this value. Neither of these variations appears if additional severe mitral or aortic lesions are present. The authors tested the validity of these statements in 6 patients with pure mitral stenosis and 11 patients in whom mitral stenosis was associated with significant regurgitation of the mitral or aortic valve (all with atrial fibrillation). In general, the findings were in agreement with the above statements in the literature, variations of the 2 phonocardiographic intervals occurring concommitantly and to about the same degree. There were, however, several important exceptions, both in the absence and in the presence of mitral insufficiency. These are ascribed by the authors to the degree of flexibility of the mitral valve.

PICK

Prinzmetal, M., Goldman, A., Massumi, R. A., Rakita, L., Schwartz, L., Kennamer, R., Kuramoto, K., and Pipberger, H.: Clinical Implications of Errors in Electrocardiographic Interpretation. J.A.M.A. **161:** 138 (May 12), 1956.

A symptom complex described under the term "heart disease of electrocardiographic origin" is characterized by subjective symptoms of heart disease and marked anxiety occasioned or intensified by an inaccurate interpretation of the electrocardiogram. Electrocardiographic misinterpretations have occurred in the past and will continue to occur in the future owing to the paucity of knowledge concerning the genesis of the electrocardiographic components and to uncertainties involving the range of the normal. Too many physicians expect a tracing to make the diagnosis of heart disease for them, and in so doing underestimate the value of other important clinical data. The 2 most important symptoms of heart disease of electrocardiographic origin are anxiety and chest pain. Tenderness on firm fingertip pressure over the anterior chest wall is the most significant finding on physical examination. A correct diagnosis depends on the physicians high index of suspicion and on the awareness of 2 facts. First, chest pain does not always represent heart disease. Secondly, S-T segment and T-wave changes do not invariably denote myocardial abnormality and may sometimes be caused by the patient's fear or apprehension. Treatment consists of prophylactic and therapeutic measures. The phrase "these changes may also occur in patients with normal hearts" should be added to the interpretation of the tracings with equivocal S-T segment and T-wave changes. Curative therapy consists chiefly of reassurance. While the electrocardiogram is one of the most useful diagnostic aids, its interpretation is often fraught with considerable uncertainty and for this reason the clinical state of the patient with symptoms referable to the heart remains the most reliable guide in diagnosis and management.

KITCHELL

Prinzmetal, M., Kennamer, R., Weiner, S. M., and Bishop, J. R.: High-Speed Cineradiography and Electrocardiography. J.A.M.A. **161:** 1229 (July 28), 1956.

Motion pictures of the heart as it appears in fluoroscopy can be made by using a camera in connection with an image-intensifying tube. Pictures can be greatly slowed for study so that the events of 1 second take almost 14 seconds to view on the screen. Therefore, detailed study of the movements of the heart shadow can be made, since the electrocardiogram, ballistocardiogram, phonocardiogram, or any other record transmissible to an oscilloscope can be photographed in synchronism with the heart shadow. As technics are improved by the development of more powerful image intensifiers, faster lenses, better cameras, and more sensitive film, more information will be obtained by this procedure. The procedure is a promising one by which valuable diagnostic information can be obtained without subjecting the patient to any inconvenience.

KITCHELL

AMERICAN HEART ASSOCIATION, INC.

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AHA FELLOWSHIP APPLICATIONS DUE BY SEPTEMBER 15

September 15 is the deadline for submitting applications for research fellowships and established investigatorships to be supported by the Association during the fiscal year beginning July 1, 1958. Applications for grants-in-aid during the same period must be received by the Association no later than November 1, 1957.

All applications must be made on forms available from the Association's Assistant Medical Director for Research. The following awards are involved: Research Fellowships ranging from $3,800 to $5,700; Advanced Research Fellowships, $4,600 to $6,500; Established Investigatorships, from $6,000 to $8,000. Classification as Research or Advanced Research Fellow is at the discretion of the Association's Research Committee.

225 GRANTS BRING 1957 RESEARCH SUPPORT TO TOTAL OF $2,372,285

Two hundred and twenty-five investigators working in the cardiovascular field have been awarded grants-in-aid under the research support program of the American Heart Association and its affiliates. These grants, totalling $1,395,285, brought to 380 the number of research awards made by the Association this year. Previously announced were 155 fellowships in the amount of $977,000. These grants-in-aid together with the earlier fellowships have a vlaue of $2,372,285. This support program is financed from public contributions to the Heart Fund.

The 1957 series constitutes the largest single group of research awards in the Association's history. The total amount awarded to research last year exceeded $1,870,000. Two years ago, a total of $1,414,000 was awarded for research fellowships and grants-in-aid.

In addition to the 1957 fellowships and grants awarded by the American Heart Association, state and local Heart Associations are supporting research activities in their own areas. The size of these awards will not be known until later this year.

A complete list of grants-in-aid follows at the end of this section.

AHA ANNUAL MEETING AND SCIENTIFIC SESSIONS

Howard B. Sprague, M.D., Boston, former President of the Association, will serve as Chairman of the Special Scientific Session for Physicians in General Medicine which precedes the regular Scientific Sessions of the association on Friday, October 25.

The 30th Scientific Sessions, Saturday, October 26 through Monday morning, October 28, will commemorate the tercentenary of the death of William Harvey. They will be held as part of the Association's 33rd Annual Meeting at the Hotel Sherman in Chicago.

The highlights of the four-day scientific program, and of the Annual Meeting, which will extend through Tuesday morning, are as follows:

Friday morning, October 25: The special program for general practitioners will include presentations on various aspects of "Prevention and Management of Cardiovascular Emergencies." Participants in the morning session and their specialized topics will include James M. Metcalfe, M.D., Boston, emergencies in pregnancy; Benjamin M. Gasul, M.D., Chicago, emergencies in children; Robert A. Hingson, Jr., M.D., Cleveland, emergencies during anesthesia; Louis A. Soloff, M.D., Philadelphia, emergencies after surgery; Maurice K. Sokolow, M.D., San Francisco, emergencies during drug therapy; and Stewart G. Wolf, Jr., M.D., Oklahoma City, emergencies in anxiety states.

Questions arising from the morning program will be answered during a one-hour discussion period in the afternoon. A panel on "Unsettled Questions in the Management of Cardiovascular Disease" will conclude the all-day program. Louis M. Katz, M.D., Chicago, will moderate this panel. Participants will be Drs. George E. Burch, New Orleans; Albert Dorfman, Chicago; A. Carlton Ernstene, Cleveland; Hans H. Hecht, Salt Lake City; and Robert L. Parker, Rochester, Minnesota. *Evening:* A special session on "Instrumental Methods in Cardiovascular Diagnosis."

Saturday morning, October 26: General session which will feature the Lewis A. Conner Memorial Lecture by Charles Rammelkamp, Jr., M.D., Cleveland, and the presentation of the Albert Lasker Award of the American Heart Association. The Association's Council on Rheumatic Fever and Congenital Heart Disease will hold its annual luncheon. *Afternoon:* Simultaneous Scientific Sessions of the Councils on Clinical Cardiology, Circulation, Basic Science, and Rheumatic Fever and Congenital Heart Disease.

Sunday morning, October 27: General Session, including the George E. Brown Memorial Lecture by Nelson W. Barker, M.D., Rochester, Minn., on "The Current Evaluation of the Thrombosis Problem." The Community Service and Education Council will hold its annual luncheon. *Afternoon:* Joint program of the Community Service and Education Council and the Staff Conference of Heart Associations on "Community Service —Its Nature and Its Significance for Heart Associations." In addition, the Council will sponsor a scientific panel, to be organized by Herbert Pollack, M.D., Chairman of the Association's Nutrition Committee, on "Lipid Metabolism and Arteriosclerosis." Among the participants in the panel will be Herman Hilleboe, M.D., New York State Commissioner of Health, Oglesby Paul, M.D., Chicago, Clinical Associate Professor of Medicine, University of Illinois College of Medicine, and Robert Eugene Olson, M.D., Professor of Biochemistry and Nutrition, Graduate School of Public Health, Pittsburgh. *Evening:* Annual Dinner of the American Heart Association including the presentation of Gold Heart Awards.

Monday morning, October 28: Simultaneous Scientific Sessions of the Councils on Cardiovascular Surgery and High Blood Pressure Research.

Six Assembly Panels will be in session on Monday. They will discuss the following subjects: Research; Fund Raising and Public Relations; Relationships and Responsibilities Between National, State and Local Heart Associations; Community Service; Heart Association Support of Medical Schools; Heart Association Services to Professional Groups.

Tuesday morning, October 29: Annual Session of the Association's general Assembly which will review panel recommendations and elect officers and Board members of the Association.

ASSOCIATION CREATES CENTRAL COMMITTEE FOR MEDICAL & COMMUNITY PROGRAMS

The Board of Directors of the American Heart Association authorized the creation of a new Central Committee for Medical and Community Programs at its June meeting. This Committee is to be headed by the immediate Past President of the Association and will report directly to the Board of Directors or its Executive Committee.

It will be the function of this committee to make the most effective use of all the broad scientific, medical and professional interests, as represented in the various Councils and Committees.

Membership of the new Central Committee will include the Chairmen of seven Councils —the Councils on Rheumatic Fever and Congenital Heart Disease, High Blood Pressure Research, Circulation, Cardiovascular Surgery, Basic Science, Clinical Cardiology, and Community Service and Education.

Other members will include the Chairmen of the following Committees: Research, Publications, Review Research Policy, Professional Education, Clinics, Program of Scientific Meetings, Nutrition, Program Evaluation, Education and Rehabilitation.

HIGH BLOOD PRESSURE COUNCIL PROCEEDINGS AVAILABLE

A bound volume containing the proceedings of the 1956 annual meeting of the Association's Council for High Pressure Research is now available from the American Heart Association. This volume has approximately 80 pages and 15 illustrations and is priced at $2.75.

The Council's 1956 annual meeting took place in Cleveland last November 30–December 1. The following papers are included among the scientific reports: *Studies on the Hypertensive Action of Adrenal Steroids*, by Abbie I. Knowlton, M.D.; *Studies on the Pathogenesis of the Hypertensive Vascular Disease which Occurs in Rats Bearing Regenerating Adrenal Cortical Tissue*, by Floyd R. Skelton, M.D.; *Studies on the Revascularized Kidney*, by Yale J. Katz, M.D.; *The Electron Microscopy of the Kidney*, by Daniel C. Pease, Ph.D.; and *Some Factors Influencing the Renal Excretion of Sodium and Water*, by H. P. White, M.D.

Among the reports to the public are papers by Drs. A. C. Corcoran on *Recent Advances in Hypertension and Atherosclerosis*; G. E. Wakerlin, *Recent Advances in Hypertension*; Levin L. Waters, *High Blood Pressure, Damage to Arteries, Arteriosclerosis: An Experimental Study*; and Edward Weiss, *The Emotional Problems of Coronary Occlusion.*

LIFE INSURANCE FUND OFFERS RESEARCH FELLOWSHIPS AND GRANTS

Applications for awards available July 1, 1958, will be received by the Life Insurance Medical Research Fund as follows:

1. *Until October 15, 1957*, for post-doctoral research fellowships. Candidates may apply for support in any field of the medical sciences. Preference is given to those who wish to work on cardiovascular function and disease or related fundamental problems. Maximum stipend is $3,800, with allowances for dependents and necessary travel.

2. *Until November 1, 1957*, for grants to institutions in aid of research on cardiovascular problems. Support is available for physiological, biochemical, and other basic work broadly related to cardiovascular problems as well as for clinical research in this field.

Further information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 345 East 46th Street, New York 17, N. Y.

ASSOCIATION ISSUES SERIES OF THREE SHORT FILMS

"Strokes," the third in a series of three short color films is now available from the national office or through local Heart Associations. The first in the series deals with coronary heart disease and the second with high blood pressure. All three films are approximately six minutes long and can be used for television or direct audience viewing. They provide an excellent visual aid to physicians addressing lay groups.

The films, which use a combination of animated drawings, live photography and diagrams, were produced by Churchill-Wexler for the American Heart Association.

MEETINGS CALENDAR

September 8–13: American Congress of Physical Medicine & Rehabilitation, Los Angeles. Frances Baker, 1 Tilton St., San Mateo, Calif.

September 9–12: U. S. Section, International College of Surgeons, Chicago, Ill. Karl Meyer, 1516 Lake Shore Drive, Chicago, Ill.

September 23–25: Symposium on Peripheral Vascular Disease, Minn. Heart Association and Mayo Foundation, Rochester, Minn. Guy W. Daugherty Mayo Clinic, Rochester, Minn.

September 29–October 4: College of American Pathologists, New Orleans, La. A. H. Dearing, Prudential Plaza, Suite 2115, Chicago 1, Ill.

October 1–4: American Roentgen Ray Society, Washington, D. C. Barton R. Young, Germantown Hospital, Philadelphia 44, Pa.

October 7–10: American Academy of Pediatrics, Chicago, Ill. E. H. Christopherson, 1801 Hinman Ave., Evanston, Ill.

October 14–18: American College of Surgeons, Atlantic City, N. J. Michael L. Mason, 40 E. Erie St., Chicago 11, Ill.

October 14–19: American Society of Anesthesiologists, Los Angeles, Calif. J. E. Remlinger, Jr., 188 W. Randolph St., Chicago 1, Ill.

October 18–21: Third International Congress of The International Society of Angiology, Ambassador Hotel, Atlantic City, N. J. Dr. Henry Haimovici, 105 E. 90th St., New York 28, N. Y.

October 21–23: Association of American Medical

Colleges, Atlantic City, N. J. Dean F. Smiley, 2530 Ridge Ave., Evanston, Ill.

October 23–25: American Association of Medical Clinics, Kansas City, Mo. Harold D. Caylor, Caylor-Nickel Clinic, Bluffton, Ind.

October 25–28: Scientific Sessions of the American Heart Association, Chicago, Ill. American Heart Association, 44 East 23rd St., New York 10, N. Y.

November 1–9: School Health Association, Washington, D. C. M. F. Shanholtz, M.D., State Office Bldg., Richmond, Va.

November 3–4: American Society for the Study of Arteriosclerosis, Chicago, Ill. O. J. Pollak, M. D., P.O. Box #228, Dover, Del.

November 11–15: American Public Health Association, Cleveland, Ohio. R. M. Atwater, M.D., 1790 Broadway, New York 19, N.Y.

November 17–22: Radiological Society of North America, Chicago, Ill. D. S. Childs, M.D., 713 E. Genesee St., Syracuse 2, N.Y.

December 3–6: American Medical Association, Philadelphia. George F. Lull, 535 N. Dearborn St., Chicago 10., Ill.

ABROAD

September 29–October 5: World Medical Association, Istanbul, Turkey. Louis H. Bauer, M.D., 10 Columbus Circle, New York 19, N.Y.

October 27–November 2: Congress of International Society of Surgery, Mexico City, Mexico. Dr. L. Dejardin, 141, rue Belliard, Brussels, Belgium.

September 14–21, 1958: Third World Congress of Cardiology, Brussels. Dr. F. Van Dooren, 80 Rue Mercelis, Brussels, Belgium.

LIST OF GRANTS

Following is a complete list of recipients of 1957 grants-in-aid awarded by the American Heart Association, together with the institutions at which the scientists are working and the subjects of their studies:

Continued Grant Awards

Frederick W. Barnes, Jr., M.D., Ph.D., The Johns Hopkins Hospital, Baltimore, Md., for the study of regenerative cellular response to induced depletion of cellular proteins.

Richard J. Bing, M.D., Washington University Medical Service and Veterans Administration Hospital, St. Louis, Missouri, for myocardial metabolism; Studies on contractile proteins of the failing heart.

Gerhard A. Brecher M.D., Ph.D., The Ohio State University College of Medicine, Columbus, Ohio, for the study of dynamic aspects of blood flow in physiological and pathological states.

Leon Churney, Ph.D., Louisiana State University School of Medicine, New Orleans, La., to study the electrical properties of normal and vagally inhibited atrial muscle.

Loyal L. Conrad, M.D., The University of Oklahoma School of Medicine and University Hospitals, Oklahoma City, Okla., to study the order of activation of the free wall of the right ventricle in experimental right bundle-branch block.

R. Duncan Dallam, Ph.D., University of Louisville School of Medicine, Louisville, Ky., for the investigation of certain biochemical responses of the various regions of the heart muscle to experimental hypo- and hyperthyroidism.

William Drell, Ph.D., Veterans Administration Center, Los Angeles, Calif., for studies on the nature of the immediate precursors of sympathin.

Douglas R. Drury, M.D., Kerckhoff Laboratories, University of Southern California School of Medicine, Los Angeles, Calif., for the investigation of genetic and environmental factors in the production of hypertension; cardiovascular responses and effects of lowering blood pressure of spontaneously hypertensive rabbits.

Isidore S. Edelman, M.D., University of California, Metabolic Isotopic Laboratories, San Francisco City and County Hospital, San Francisco, Calif., for the study of fluid and electrolyte anatomy in patients with essential hypertension.

J. Russell Elkinton, M.D., University of Pennsylvania School of Medicine, Philadelphia, Pa., for the study of body composition and extracorporeal dialysis in edematous patients with cardiovascular-renal disease.

Franklin H. Epstein, M.D., Yale University School of Medicine, New Haven, Conn., for the study of factors influencing renal concentrating ability.

Frank A. Finnerty, Jr., M.D., Georgetown University Medical Division, District of Columbia General Hospital, Washington, D. C., to study the cardiovascular evaluation of delerium tremens.

Meyer Friedman, M.D., Harold Brunn Institute, Mount Zion Hospital, San Francisco, Calif., for further studies concerning the metabolism of cholesterol.

Mario Gaudino, M.D., Ph.D., New York University College of Medicine, New York, N. Y., to study the water and electrolyte exchanges in tissues.

Robert A. Good, M.D., Ph.D., University of Minnesota Medical School, Minneapolis, Minn., to study the basic mechanisms involved in etiology and pathogenesis of rheumatic fever and related diseases.

Carl W. Gottschalk, M.D., University of North Carolina School of Medicine, Chapel Hill, N. C., to study the mammalian micropuncture study of some of the physical factors in kidney function.

Robert E. Gross, M.D., The Children's Hospital,

Boston, Mass., for studies relevant to surgical treatment of congenital heart disease.

Jacob Grossman, M.D. Montefiore Hospital, New York, N. Y. for (1) Studies on the response of cardiac patients to mercurial diuretics with particular reference to the tubular adaptations to reduced filtration rate in congestive heart failure; (2) Studies on cardiovascular-renal mechanisms regulating body fluid volume in man.

Tom R. Hamilton, M.D., University of Kansas Medical Center, Children's Convalescent Center and Kansas City-Wyandotte County Health Department, Kansas City, Kan., for a community-type study of children in rheumatic and non-rheumatic families.

Calvin Hanna, Ph.D., University of Vermont College of Medicine, Burlington, Vt., for studies on tachyphylaxis.

Walter Heymann, M.D., University Hospitals, Western Reserve University School of Medicine, Cleveland, Ohio, to study the regulation of blood lipid concentration with special reference to pathogenesis of nephrotic hyperlipemia.

Nathan O. Kaplan, Ph.D., Brandeis University, Waltham, Mass., for the study of metabolic significance of nucleotides in cardiovascular tissues.

Louis N. Katz, M.D., Medical Research Institute, Michael Reese Hospital, Chicago, Ill., for the study of coronary circulation, cardiac energetics and myocardial metabolism.

F. E. Kelsey, Ph.D., University of South Dakota School of Medicine, Vermillion, S. D., to study the mechanism of action of digitoxin and related substances.

Grace P. Kerby, M.D., Duke University School of Medicine, Durham, N. C., to study the metabolism of acid mucopolysaccharides of ground substance.

Peter T. Kuo, M.D., Hospital of the University of Pennslyvania and the University of Pennsylvania School of Medicine, Philadelphia, Pa., for the investigation of vascular fluid dynamics, their influences upon the intra-vascular distribution of plasmalipids and their relationship to the problem of atherosclerosis.

Willoughby Lathem, M.D., University of Pittsburgh School of Medicine, Pittsburgh, Pa., for studies on glomerular permeability to hemoglobin.

Abel A. Lazzarini, Jr., M.D., New York University, Post-Graduate Medical School, New York, N. Y., for the studies of the metabolic and immunological changes occurring in transplanted tissues.

Alexander Leaf, M.D., Massachusetts General Hospital, Boston, Mass., to study the state of body water.

Eugene Lepeschkin, M.D., University of Vermont College of Medicine, Burlington, Vt., for the study of differentiation between organic and functional systolic murmurs by means of esophageal calibrated phonocardiography, correlated with blood viscosity.

Maurice Lev, M.D., Mount Sinai Hospital of Greater Miami, Miami Beach, Florida, to study the histopathology of the conduction system in congenital heart disease.

Averill A. Liebow, M.D., Yale University School of Medicine, New Haven, Conn., for quantitative comparative studies of experimentally induced collateral circulation to the heart.

William D. Lotspeich, M.D., University of Cincinnati College of Medicine, Cincinnati, Ohio, to study the relation between intermediary metabolism in the kidney and several of its excretory functions.

James W. McCubbin, M.D., Cleveland Clinic Foundation, Cleveland, Ohio, to study neural mechanisms in experimental renal hypertension.

Henry D. McIntosh, M.D., Duke University School of Medicine, Durham, N. C., to study the responses of the pulmonary and systemic circulation to changes of intrathoracic pressure.

Edward Meilman, M.D., Long Island Jewish Hospital, New Hyde Park, Long Island, N. Y., for the study of the contractile apparatus in smooth muscle.

John P. Merrill, M.D., Peter Bent Brigham Hospital, Boston, Mass., for an investigation of the relation of renal failure to certain disorders of the cardiovascular system.

William R. Milnor, M.D., The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital, Baltimore, Md., to study the regional blood volumes in congenital and acquired heart disease.

Wilfried F. H. M. Mommaerts, Ph.D., University of California Medical Center, Los Angeles, Calif., for the study of chemical-physiological and biophysical studies related to the problem of contractility.

Merwin Moskowitz, Ph.D., Purdue University, Lafayette, Ind., for studies on an antigen of streptococci that binds on to tissues.

Robert E. Olson, M.D., Ph.D., University of Pittsburgh, Graduate School of Public Health, Pittsburgh, Pa., to study the effect of congestive heart failure due to valvular disease upon myocardial metabolism in dogs.

J. Lowell Orbison, M.D., University of Rochester School of Medicine and Dentistry, Rochester, N. Y., to study the relationship of the kidney to membrane permeability and fluid and electrolyte distribution in experimental hypertensive cardiovascular disease.

John J. Osborn, M.D., Stanford University School of Medicine, Stanford University Hospitals, San Francisco, Calif., to study the diagnosis and surgical treatment of congenital and acquired heart disease: Extracorporeal circulation, gaso-

metric analyses of flows and shunts; Cardiorespiratory physiology in open-chest surgery.

Abraham G. Osler, Ph.D., The Johns Hopkins University School of Hygiene and Public Health, Baltimore, Md., for studies on the mechanism of hypersensitivity reactions.

Ely Perlman, M.D., The Mount Sinai Hospital, New York, N. Y., for the role of tobacco allergy in the etiology of cardiovascular diseases.

Simon Rodbard, M.D., Ph.D., The University of Buffalo Chronic Disease Research Institute, Buffalo, N. Y., to study the dietary patterns in the development and regression of experimental arteriosclerosis.

Ray H. Rosenman, M.D., Harold Brunn Institute, Mount Zion Hospital, San Francisco, Calif., for the study of the mechanism of hypercholesteremia and hyperlipemia in experimental nephrosis in rats.

Abraham M. Rudolph, M.D., The Children's Medical Center, Boston, Mass., to study the pulmonary hypertension in congenital heart disease.

David D. Rutstein, M.D., Harvard University Medical School, Boston, Mass., to study the effects of rheumatic fever serum and steroid compounds on human heart muscle in tissue culture.

David D. Rutstein, M.D., Cooperative Rheumatic Fever Study, American Heart Association, New York, N. Y., to study the relative effectiveness of ACTH, cortisone and aspirin therapy of rheumatic fever in the prevention of rheumatic heart disease.

D. Rao Sanadi, Ph.D., University of California School of Medicine, Berkeley, Calif., for the mechanism of α-ketoglutarate oxidation and coupled phosphorylation.

Allen M. Scher, Ph.D., University of Washington School of Medicine, Seattle, Wash., to study body surface potentials produced by an intracardiac dipole.

Bodil Schmidt-Nielsen, D.D.S., Duke University School of Medicine, Durham, N. C., for the comparative studies on the renal function in various animals with special emphasis on the mechanism for urea excretion as related to protein metabolism.

William B. Schwartz, M.D., New England Center Hospital, Boston, Mass., to study the acid-base regulation by the kidney and tissues.

Belding H. Scribner, M.D., Veterans Administration Hospital, King County Hospital and University of Washington School of Medicine, Seattle, Wash., for further studies on practical problems in the management of fluid electrolyte therapy.

Arthur J. Seaman, M.D., University of Oregon Medical School, Portland, Ore., for a controlled long-term study of continuous anticoagulant therapy in coronary artery disease.

Alvin P. Shapiro, M.D., University of Pittsburgh School of Medicine, Pittsburgh, Pa., for a controlled study in the rat of the relationship between hypertensive vascular disease and experimental chronic pyelonephritis.

Alan C. Siegel, M.D., The Children's Memorial Hospital, Chicago, Ill., for studies on the incidence, diagnosis, treatment and non-suppurative complications of group A streptococcal infections in a general pediatric population, with particular reference to the attack rate and prevention of rheumatic fever.

Daniel H. Simmons, M.D., Ph.D., Veterans Administration Center, West Los Angeles, Calif., to study the role of the bronchomotor tone in the etiology of cor pulmonale.

Thomas P. Singer, Ph.D., Edsel B. Ford Institute for Medical Research, Henry Ford Hospital, Detroit, Mich., for: A. The succinic oxidase of the heart muscle: B. Mechanism of SO_2 fixation in animal tissues.

Marvin D. Siperstein, M.D., Ph.D., University of Texas Southwestern Medical School, Dallas, Tex., for the studies on factors influencing the destruction of cholesterol.

Merrill P. Spencer, M.D., Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C., to study the direct measurement of blood flow in humans.

Jeremiah Stamler, M.D., Medical Research Institute, Michael Reese Hospital, Chicago, Ill., to study the pathophysiological homeostasis of renal function and water-electrolyte metabolism in experimental congestive circulatory failure with edema.

Mario Stefanini, M.D., Saint Elizabeth's Hospital, Brighton, Mass., for the identification and purification of substances causing the activation of fibrinolysin in man and their use in the control and treatment of thromboembolic conditions.

Leon Swell, Ph.D., Veterans Administration Hospital, Martinsburg, W. Va., to study the mechanism of cholesterol absorption and its regulation in the blood.

Albert Szent-Györgyi, M.D., Ph.D., Institute for Muscle Research, Marine Biological Laboratory, Woods Hole, Mass., to study the chemical macromolecular and histological structure of muscle and chemistry of contraction cycle; mechano-chemical coupling.

Helen B. Taussig, M.D., Cardiac Clinic-Harriet Lane Home, The Johns Hopkins Hospital, Baltimore, Md., for research on etiology of congenital malformations of the heart and great vessels.

Henry L. Taylor, Ph.D., Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minn., to study the physical activity and degenerative heart disease, particularly the use of railroad retirement board records to study death rates from degenerative heart disease among active and sedentary railroad employees.

Lewis Thomas, M.D., New York University College

of Medicine, New York, N. Y., to study the mechanisms of tissue damage in bacterial infection and hypersensitivity.

Louis Tobian, M.D., University of Minnesota Medical School, Minneapolis, Minn., for studies on the physiology of the renal antihypertensive mechanism in man and experimental animals.

George E. Wakerlin, M.D., Ph.D., University of Illinois College of Medicine, Chicago, Ill., to study the pathogenesis and treatment of experimental hypertension produced by constriction of the carotid sinus area.

Homer R. Warner, M.D., Ph.D., University of Utah College of Medicine, Salt Lake City, Utah, to study the physiology of the mammalian heart during complete by-pass.

William B. Wartman, M.D., Northwestern University Medical School, Chicago, Ill., for a study of the cytochemical changes that take place in the myocardium injury, with special reference to ischemia and hypertrophy.

William J. Whalen, Ph.D., University of California Medical Center, Los Angeles, Calif., for the study of cardiac efficiency.

Robert A. Woodbury, M.D., Ph.D., University of Tennessee Medical Units, Memphis, Tenn., to study the drug action on cardiac muscle with special attention to mechanism of action. Sympathomimetic amines and serotonin will be studied, using the papillary muscle technic.

Felix Wroblewski, M.D., Sloan-Kettering Institute for Cancer Research, New York, N. Y., to study the serum enzymes in relation to experimental and clinical heart disease.

Benjamin W. Zweifach, Ph.D., New York University-Bellevue Medical Center, New York, N. Y., to study the delineation of physical and chemical factors affecting blood flow and transcapillary exchange.

New Approved Grants

George H. Acheson, M.D., University of Cincinnati College of Medicine, Cincinnati, Ohio, for pharmacologic studies of cardiac glycosides and related compounds having saturated lactone rings.

Jerry K. Aikawa, M.D., University of Colorado School of Medicine, Denver Colo., for the study of immunophysiology.

Julian L. Ambrus, M.D., Ph.D., The University of Buffalo School of Medicine, Buffalo, N. Y., for studies on the lysis of radioactive clots by fibrinolytic enzymes and anticoagulants.

William G. Beadenkopf, M.D., New York State Department of Health and Albany Medical College, Albany, N. Y., to study a pathological and epidemiological investigation of coronary atherosclerosis.

David V. Becker, M.D., New York Hospital-Cornell University Medical Center, New York, N. Y., to study the physiologic effects of hypometabolism upon cardiovascular dynamics in patients with cardiac insufficiency.

Samuel Bellet, M.D., Philadelphia General Hospital, Philadelphia, Pa., for the treatment of slow heart rates and cardiac arrest with molar sodium lactate and allied chemical agents.

Gerald S. Berenson, M.D., Louisiana State University School of Medicine, New Orleans, La., for the continuation of studies of effects of inflammation on connective tissue.

Peter Bernfeld, Ph.D., Tufts University School of Medicine, Boston, Mass., for the correlation of results of lipoprotein determinations obtained by a new nephelometric method with those secured by zone electrophoresis and fractional ultracentrifugal flotation.

Maurice M. Best, M.D., Institute for Medical Research, University of Louisville, Louisville, Ky., for the study of hypocholesterolemic agents by means of tracer technics.

Reinhard H. Beutner, M.D., Ph.D., Des Moines Still College of Osteopathy and Surgery, Des Moines, Iowa, for study on electro-biochemistry as the basis of cardiac therapy.

William S. Blakemore, M.D., University of Pennsylvania School of Medicine, Philadelphia, Pa., for the evaluation of freeze-dried homografts and synthetic cloth mesh materials used to replace human blood vessels.

Edward H. Bloch, M.D., Ph.D., Western Reserve University School of Medicine, Cleveland, Ohio, to study the sequential biophysical analysis of the effect of antigen-antibody reactions on the microcirculation and blood vessel walls in vivo.

J. M. B. Bloodworth, Jr., M.D., The Ohio State University College of Medicine, Columbus, Ohio, to study the chemistry, histochemistry and renal histopathology of degenerative vascular disease associated with diabetes mellitus. A human and experimental study of the Kimmelsteil-Wilson syndrome.

Walter M. Booker, Ph.D., Howard University School of Medicine, Washington, D. C., to study the effects of hypothermia on blood electrolytes and the response of the heart to drugs during hypothermia.

Edwin Boyle, Jr., M.D., Medical College of South Carolina, Charleston S. C., for the investigation of a chemical method for measuring heparinoids in biological fluids.

Allan J. Brady, Ph.D., University of Cambridge, Cambridge, England, to study the efflux of sodium and potassium from frog ventricle.

Burtis B. Breese, M.D., University of Rochester School of Medicine and Dentistry, Rochester, N. Y., for studies of streptococcal infection in children and their relation to rheumatic fever.

Ellen Brown, M.D., University of California Medical Center, San Francisco, Calif., to study blood

volume in relation to height, weight, sex, age and physical training, and in pathologic states including obesity.

J. Marion Bryant, M.D., New York University-Bellevue Medical Center, New York, N. Y., to study the normal electrocardiogram.

Nancy M. Buckley, M.D., Albert Einstein College of Medicine of Yeshiva University, New York, N. Y., for the study of cardiodynamics and ventricular failure.

H. Mead Cavert, M.D., University of Minnesota Medical School, Minneapolis, Minn., to study the metabolism of cardiac tissue investigated with isotopic techniques; Intermediates of propionate, lactate, and pyruvate metabolism.

Fu-Chuan Chao, Ph.D., Stanford University, Stanford, Calif., for the study of ribonucleoproteins and their role in protein synthesis.

Vernon H. Cheldelin, Ph.D., Oregon State College, Corvallis, Ore., for the study of oxidative patterns and electron transport in heart muscle.

Alfred W. Childs, M.D., Stanford University School of Medicine, San Francisco, Calif., to study the effect of arterialization of the portal blood supply on the hepatic hemodynamics in dogs.

Leland C. Clark, Jr., Ph.D., Fels Research Institute, Antioch College, Yellow Springs, Ohio, to study optimum conditions for whole body perfusion.

David G. Cogan, M.D., Howe Laboratory of Ophthalmology, Harvard University Medical School, Massachusetts Eye and Ear Infirmary, Boston, Mass., to study the aging processes as reflected in the cornea, specifically the relation of fat deposition in the cornea to atheroma in the blood vessels.

Hadley L. Conn, Jr., M.D., Hospital of the University of Pennsylvania, Philadelphia, Pa., for the study of blood flow and myocardial metabolism with the aid of radio-isotope technics.

William E. Connor, M.D., State University of Iowa College of Medicine, Iowa City, Iowa, to study the effect of estrogen upon blood coagulation in men and women: Its possible relationship to atherosclerosis.

Jack W. Crowell, Ph.D., University of Mississippi, Medical Center, Jackson, Miss., to study the effect of miliary embolism on circulatory dynamics.

David W. Cugell, M.D., Cook County Chest Hospital and Northwestern University Medical School, Chicago, Ill., for the study of factors responsible for the development of cor pulmonale in chronic obstructive emphysema.

T. S. Danowski, M.D., University of Pittsburgh School of Medicine, Pittsbrugh, Pa, to study hemodialysis in chronic far advanced but not terminal renal failure.

Ralph A. Deterling, Jr., M.D., Columbia University College of physicians and Surgeons, New York, N. Y., for: (1) Continuation study of synthetic replacement of blood vessels; (2) Continued development of prostheses suitable for correction of aortic insufficiency and mitral insufficiency.

Richard A. DeWall, M.D., University of Minnesota Medical School, Minneapolis, Minn., to study direct vision intracardiac surgery.

H. E. Ederstrom, Ph.D., University of North Dakota School of Medicine, Grand Forks, N. D., for the study of epinephrine sensitivity of isolated blood vessel strips as influenced by sex hormones.

J. Russell Elkinton, M.D., University of Pennsylvania School of Medicine, Philadelphia, Pa., for studies on the supra-optico-hypophyseal system in the cat pertaining to volume and concentration regulation; an effort to provide at least a partial explanation of certain phenomena observed in markedly edematous patients with heart disease.

Alfred E. Farah, M.D., The Research Foundation of State University of New York, Syracuse, N. Y., to study the relationship of electrical phenomena, ion fluxes and contractile force in cardiac muscle as influenced by cardioactive drugs.

George Fawaz, M.D., Ph.D., American University of Beirut School of Medicine, Beirut, Lebanon, to study the effect of arrhythmias on the performance and metabolism of the isolated mammalian heart, (heart-lung preparation).

Alfred P. Fishman, M.D., Columbia University College of Physicians and Surgeons, New York, N. Y., to study the relationships between ventilation and pulmonary blood flow in normal man and in patients with chronic cardiopulmonary disease.

Ernest C. Foukes, Ph.D., The May Institute for Medical Research, Cincinnati, Ohio, for the control of intracellular electrolyte composition.

Ernst K. Franke, Dr. Ing., Cincinnati General Hospital, Cincinnati, Ohio, for the study of the peripheral circulation in health and disease by means of heat flow calorimetry.

Melvin J. Fregly, Ph.D., University of Florida College of Medicine, Gainesville, Fla., to study the sensitivity, specificity and mechanism of the spontaneous sodium chloride aversion of hypertensive rats.

Benjamin M. Gasul, M.D., Hektoen Institute for Medical Research of the Cook County Hospital, Chicago, Ill., to study the electroencephalogram in congenital malformations of the heart and in cardiac arrhythmias.

Peter C. Gazes, M.D., Medical College of South Carolina, Charleston, S. C., for the investigation of the role of heart contractile force in cardiovascular therapy.

John H. Gibbon, Jr., M.D., The Jefferson Medical College of Philadelphia, Philadelphia, Pa., for a surgical method for the revascularization of the myocardium.

William W. L. Glenn, M.D., Yale University School of Medicine, New Haven, Conn., for enzymatic dissolution of intravascular clots.

Robert P. Glover, M.D., The Presbyterian Hospital, Philadelphia, Pa., for the study of extracorporeal circulation for application in the surgery of acquired valvular heart disease.

Allan V. N. Goodyer, M.D., Yale University School of Medicine, New Haven, Conn., to study the hemodynamic and metabolic factors affecting the cardiovascular responses to circulatory stress.

Harold D. Green, M.D., Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C., to study the mechanism of and significance of epinephrine dilation (epinephrine reversal) in skeletal muscle, mesenteric and splenic arterial vascular beds.

Herbert E. Griswold, Jr., M.D., Institute of Cardiology, University of London, London, England, to observe and work with the methodology of technics utilized in clinical hemodynamics.

Arthur C. Guyton, M.D., University of Mississippi Medical Center, Jackson, Miss., to study the further development and utilization of continuous recording of cardiac output by the Fick principle.

Cameron Haight, M.D., University of Michigan Medical School, Ann Arbor, Mich., to study coronary arteriography: Evaluation of methods in experimental animals; observations in human and experimental coronary artery insufficiency.

E. Raymond Hall, Ph.D., The University of Kansas, Lawrence, Kan., to study cardiovascular disease, in free-living mammals other than man, correlated with habits, habitat and heritage.

Robert McCluskey, M.D., New York University College of Medicine, New York, N. Y., for an experimental study of the inflammatory response to autologous tissue and an experimental study of the inflammatory response to autologous and homologous tissues in combination with the products of various types of hemolytic streptococci.

Carroll A. Handley, Ph.D., Baylor University College of Medicine, Houston, Tex., for the comparison of the cardiovascular response to different vasopressor agents.

Carroll A. Handley, Ph.D., Baylor University College of Medicine Houston, Tex., for an analysis of the excretory products from mercurial diuretics and a study of possible renal enzyme inhibition produced by these agents.

K. Albert Harden, M.D., Howard University School of Medicine, Washington, D. C., to study the pulmonary and cardiac dynamics in chronic pulmonary disease.

John H. Heller, M.D., New England Institute for Medical Research Ridgefield, Conn, to study the development of synthetic estrogens designed to exert an effort on abnormal blood lipids, xanthomata, and atherosclerosis but which have virtually no sexual activity.

Robert A. Helm, M.D.. Cincinnati General Hospital, Cincinnati, Ohio, for the clinical study of a spatial electrocardiogram of thirteen leads designed to have approximately uniform electrical fields.

James A. Helmsworth, M.D., University of Cincinnati College of Medicine, Cincinnati, Ohio, for a new method to by-pass the heart for intracardiac surgery without extracorporeal oxygenation.

Robert A. Hettig, M.D., Jefferson Davis Hospital, Houston, Tex., to study serum prothrombin accelerator levels in patients with acute myocardial infarctions.

John B. Hickam, M.D., Duke University School of Medicine, Durham, N. C., to study the effect of congestive heart failure on pulmonary function in patients with lung disease.

Brian F. Hoffman, M.D., State University of New York, Downstate Medical Center, Brooklyn, N. Y., to study electrophysiology of cardiac muscle, emphasizing the effects of anodal current and injury current on the transmembrane potentials, conductivity, rhythmicity and excitability of single cardiac fibers.

William C. Holland, M.D., Vanderbilt University School of Medicine, Nashville, Tenn., to study the mechanism of action of antifibrillatory drugs.

Joseph P. Holt, M.D., Ph.D., Institute for Medical Research University of Louisville, Louisville, Ky., for (1) Studies on the venous system in dogs and man with special reference to the "collapsibility" of veins, and how this effects the pressure and flow through the venous system. (2) Studies on the residual volume of the dog's ventricle.

Roger W. Jeanloz, Ph.D., Massachusetts General Hospital, Boston, Mass., to study the chemistry and biochemistry of heparins.

Wallace N. Jensen, M.D., University of Pittsburgh School of Medicine, Pittsburgh, Pa., for in vivo studies of the sickle cell phenomenon.

Howard A. Joos, M.D., University of Southern California School of Medicine and Childrens Hospital Society of Los Angeles, Los Angeles, Calif., for studies of factors regulating blood pressure in infancy and childhood.

George L. Jordan, Jr., M.D., Baylor University College of Medicine and the Veterans Administration Hospital, Houston, Tex., for an experimental study of synthetic prosthetic replacements for blood vessels including the effect of chronic hypercholesterolemia on synthetic aortic substitutes.

Walter E. Judson, M.D., Indiana University School of Medicine, Indianapolis, Ind., to study the relationship between cardiovascular and renal responses in patients with hyperkinetic circulatory states.

Alex Kaplan, Ph.D., Medical Research Institute, Michael Reese Hospital, Chicago, Ill., to study the role of adrenal medullary and cortical hormones in the regulation of lipid metabolism.

Yale J. Katz, M.D., Ph.D., University of Southern California School of Medicine, Los Angeles, Calif., to study the augmentation of kidney function by revascularization of the kidney.

Jerome H. Kay, M.D., University of Southern California Medical School, Los Angeles, Calif., for mitral valve replacement for the treatment of mitral insufficiency.

Edward M. Kent, M.D., University of Pittsburgh School of Medicine, Pittsburgh, Pa., for extracorporeal shunt for open heart surgery, utilizing a pump oxygenator.

Ancel Keys, Ph.D., Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minn., to study the frequency of ischemic heart disease, the cholesterol-lipoprotein system and the habitual diets of populations.

Arthur Kirschbaum, M.D., Ph.D., Baylor University College of Medicine, Texas Medical Center, Houston, Tex., to study the effect of the adrenal gland on obesity in mice.

William H. Knisely, Ph.D., Duke University School Of Medicine, Durham, N. C., for an in vivo evaluation of the effects of currently employed therapeutic agents on the pulmonary blood vessels and alveoli of laboratory mammals.

Charles E. Kossmann, M.D., New York University College of Medicine, New York, N. Y., for the correlation of intracellular potential variations of the single ventricular fiber with mechanical function of the ventricles.

Otto Krayer, M.D., Harvard University Medical School, Boston, Mass., for a comparative study of the chronotropic cardiac action of the rauwolfia alkaloids and related substances.

William J. Kuhns, M.D., University of Pittsburgh Medical Center, Pittsburgh, Pa., for immunochemical studies of human diphtheria antitoxins—investigation of toxin-antitoxin complexes.

Louis Leiter, M.D., Ph.D., Montefiore Hospital, New York, N. Y., for studies on potentiation of mercurial diuresis in patients with intractable chronic congestive failure.

David H. Lewis, M.D., Philadelphia General Hospital, Philadelphia, Pa., to study the transmission of sound and ultrasound in the heart: Use in the measurement of chamber size, detection of congenital defects, and characterization of murmurs.

J. Maxwell Little, Ph.D., Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C., for the study of the excretion of epinepherin, norepinephrine, and 5-hydroxyindoleacetic acid in essential hypertension and experimental hypertension resulting from partial carotid sinus clamping.

Daniel S. Lukas, M.D., Cornell University Medical College, New York, N. Y., to study the quantitation of valvular insufficiency.

W. O. Lundberg, Ph.D., University of Minnesota, The Hormel Institute, Austin, Minn. and Mayo Foundation, Rochester, Minn., to study the fat metabolism in relation to atherogenesis.

Richard A. MacDonald, M.D., Mallory Institute of Pathology, Boston City Hospital, Boston, Mass., for an attempt to reproduce experimentally valvular lesions of the heart in rats using long-term injections of serotonin (5-hydroxytryptamine) and the serotonin precursor substance 5- hydroxytryptophan.

Henry C. McGill, Jr., M.D., Louisiana State University School of Medicine, New Orleans, La., to study electron microscopy of vascular lesions.

Joseph M. McKenna, Ph.D., Seton Hall University, South Orange, N. J., to study the mechanisms of protection against circulatory collapse in hemorrhage and trauma.

Samuel Mallov, Ph.D., The Research Foundation of State University of New York, Syracuse, N. Y., for the study of the reactivity of isolated strips and of the contractile proteins of the smooth muscle of blood vessels of experimental hypertensive animals.

James V. Maloney, Jr., M.D., University of California Medical Center at Los Angeles, Los Angeles, Calif., for the investigation of l-norepinephrine as a cause of hypovolemia; study on a clinical method permitting the sudden discontinuance of the drug.

Robert H. Maybury, Ph.D., University of Redlands, Redlands, Calif., to study the physical chemistry of proteins in non-aqueous solvents, including anhydrous hydrogen fluoride and deuterium oxide.

William F. Mazzitello, M.D., Ancker Hospital, St. Paul, Minn., to study the determination and evaluation of intra pulmonary vascular shunts in laennec cirrhosis by dye dilution curve techniques and the effect of such shunts on cardiovascular hemodynamics as determinedly cardiac catheterization.

Milton Mendlowitz, M.D., The Mount Sinai Hospital, New York, N. Y., to study the digital circulation in hypertension.

H. C. Meng, M.D., Ph.D., Vanderbilt University School of Medicine, Nashville, Tenn., for the production of lipemia clearing factor(s) and its roll in lipid metabolism and atherogenesis.

Frederic C. Moll, M.D., University of Washington School of Medicine, Seattle, Wash., for the study of isolation and description of the serum proteolytic enzyme inhibitor.

George C. Morris, Jr., M.D., Baylor University College of Medicine, Houston, Tex., to study the effects of hydration, shock and anoxia on the nephrotoxic propensity of Urokon and hemolysed blood.

Peter V. Moulder, M.D., The University of Chicago, Chicago, Ill., to study the histochemical characterization of myocardium in homografts.

John H. Moyer, M.D., Jefferson Davis Hospital and Baylor University College of Medicine, Houston, Tex., for an evaluation of the long-term effect of hypertension on the kidney in untreated patients as compared to those in whom the blood pressure was effectively reduced with anti-hypertensive agents.

Russell M. Nelson, M.D., Ph.D., University of Utah College of Medicine, Salt Lake City, Utah, to study a method for the determination of blood loss during surgical procedures, employing "washed field" technic.

W. Lewis Nobles, Ph.D., University of Mississippi, University, Miss., to study the synthesis of some possible antiserotonin agents.

Jan Nyboer, D.Sc., M.D., Harper Hospital, Detroit, Mich., for the adaptation of an aperiodic frictionless suspension for study of cardiorespiratory ballistics.

Richard R. Overman, Ph.D., University of Tennessee College of Medicine, Memphis, Tenn., to study mechanisms of ionic distribution in experimental cardiovascular disorders.

James C. Owens, M.D., University of Colorado Medical Center, Denver, Colo., for experimental chronic myocardial insufficiency produced by coronary artery embolization.

Jacques Padawar, Ph.D., Albert Einstein College of Medicine of Yeshiva University, New York, N. Y., for physiology of the mast cell and its relation to cardiovascular function and disease.

William B. Parsons, Jr., M.D., Jackson Clinic, Madison, Wis., for reduction of blood cholesterol levels by administration of nicotinic acid (niacin).

H. Mitchell Perry, Jr., M.D., Washington University School of Medicine, St. Louis, Mo., to study the relation of trace metals to atherosclerosis.

Hubert V. Pipberger, M.D., Georgetown University Medical Center, Washington, D. C., for the study of orthogonal vectorcardiography and electrocardiography.

Kurt R. Reissmann, M.D., University of Kansas Medical Center, Kansas City, Kan., to study the quantitative relationship of tissue hypoxia and cellular impairment.

James A. Richardson, Ph.D., Medical College of South Carolina, Charleston, S. C., for studies of plasma concentrations of epinephrine and norepinephrine and related changes in cardiovascular function.

Jonas E. Richmond, Ph.D., Harvard University Medical School, Boston, Mass., for the role of the prosthetic group of proteins in the biosynthesis and metabolism of conjugated proteins.

Edward Ronwin, Ph.D., University of Southern California School of Medicine, Los Agneles, Calif., for the study of the enyzmes involved in blood clotting and their mechanism of action.

John C. Rose, M.D., Georgetown University Medical Center, Washington, D. C., for pulmonary vasomotor activity.

Harvey S. Rosenberg, M.D., Texas Children's Hospital, Houston, Tex., for structural and histochemical changes in the small pulmonary arteries in association with normal maturation and maturation complicated by congenital malformations of the heart.

Robert F. Rushmer, M.D., University of Washington School of Medicine, Seattle, Wash., to study the factors influencing diastolic filling and systolic emptying of the ventricular chambers.

Milton S. Saslaw, M.D., National Children's Cardiac Hospital, Miami, Fla., to study the efficacy of medication with antibiotics in eliminating beta hemolytic streptococcus from deep tissues.

Carl. F. Schmidt, M.D., University of Pennsylvania School of Medicine, Philadelphia, Pa., for the study of physiology and pharmacology of the coronary circulation, with special reference to the influence of mechanical and nervous factors.

Henry A. Schroeder, M.D., Brattleboro Retreat, Brattleboro, Vt., for studies on the reversibility of atherosclerosis.

Alvin L. Sellers, M.D., Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles, Calif., for metabolic studies on the isolated perfused mammalian kidney.

Arthur Selzer, M.D., Stanford University School of Medicine, San Francisco, Calif., to study the physiology and pharmacology of experimental cardiogenic shock.

John T. Sharp, M.D., The Buffalo General Hospital, Buffalo, N. Y., for a study of the physical properties of the lungs in pulmonary edema.

Bernard Shore, Ph.D., Medical College of Georgia, Augusta, Georgia, to study the chemistry of heparin-catalyzed lipoprotein transformations.

Herbert O. Sieker, M.D., Duke University School of Medicine, Durham, N. C., for the study of the pressure in the venous and pulmonary circulation using a miniature manometer catheter.

Jay A. Smith, Ph.D., The Chicago Medical School, Chicago, Ill., to study the effect of various metabolic blocking agents on changes in metabolic rate produced by digitalis.

Richard T. Smith, M.D., University of Texas Southwestern Medical School, Dallas, Tex., for changes in mechanisms of resistance and immunity related to age, particularly in regard to group A streptococcal infection.

Harry Sobel, Ph.D., University of Southern California School of Medicine, Los Angeles, Calif., for investigation of the cellular proteins of heart tissue.

Paul Starr, M.D., University of Southern California School of Medicine and Los Angeles County Hospital, Los Angeles, Calif., to study the response

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Borys Surawicz, M.D., University of Vermont College of Medicine, DeGoesbriand Memorial Hospital and The Mary Fletcher Hospital, Burlington, Vt., to study the effect of potassium and calcium imbalance on the electrical and mechanical properties of the mammalian heart.

Henry Swan, M.D., University of Colorado School of Medicine, Denver, Colo., for the physiological and technical studies relating to cardiovascular surgery.

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C. Bruce Taylor, M.D., Presbyterian-St. Luke's Hospital, Chicago, Ill., for the study of atherosclerosis and lipid metabolism in the Rhesus monkey and comparative studies in man.

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John C. Vanatta III, M.D., University of Texas Southwestern Medical School, Dallas, Tex., for a further investigation of several intracellular sodium compartments which has been demonstrated in studying muscle biopsies after radioactive sodium, and radioactive sulfate injections.

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John M. Weller, M.D., University of Michigan Medical School, Ann Arbor, Mich., for the investigation of abnormalities of electrolyte metabolism and acid-base balance in hypertension.

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Hugh E. Wilson, M.D., The University of Texas Southwestern Medical School, Dallas, Tex., for the complete surgical correction of transposition of the great vessels by internal atrial shunting utilizing the pump-oxygenator.

John L. Wilson, M.D., American University of Beirut School of Medicine, Beirut, Lebanon, to study (A) the determination, using cardiac catheterization technics, of the incidence of various types of congenital heart disease in a selected group of patients from the Middle East as seen in the clinics of the American University Hospital; (B) The evaluation, using cardiac catheterization technics, of mitral stenosis pre and postoperatively.

Harrison F. Wood, M.D., Irvington House, Irvington-on-Hudson, N. Y., for epidemiological studies of methods for prevention of rheumatic fever and rheumatic heart disease.

Paul N. Yu, M.D. University of Rochester School of Medicine and Dentistry, Rochester, N. Y., to study the pharmacodynamics of the pulmonary cirulation in man.

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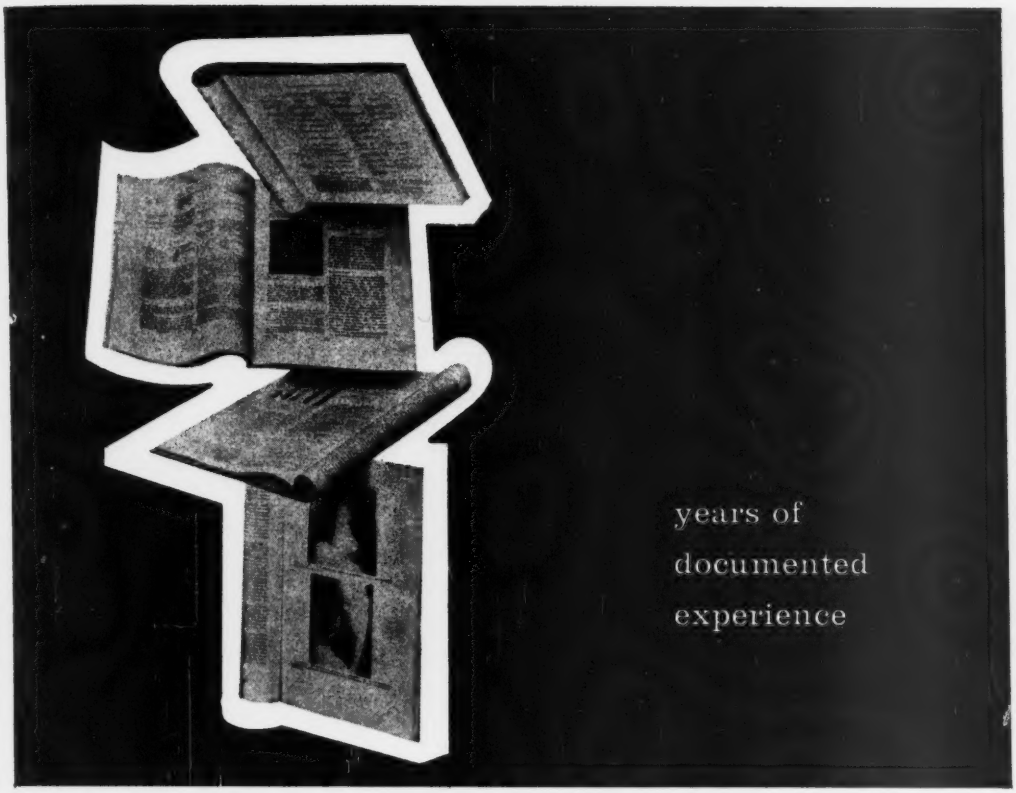

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